Postpartum women with micronutrient deficiency

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Health status and fatigue

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Contents

Chapter 1

General introduction

General introduction

During pregnancy, maternal physiological changes and fetal demands for growth and development increase the requirements of micronutrients [1]. Micronutrient deficiency, which is a common problem in both developing and developed countries [2, 3], is found to be associated with adverse neonatal and pregnancy outcomes [2, 4, 5]. Anemia can occur if there is a deficiency in iron, folic acid, or vitamin B12, since these micronutrients are needed for adequate production of red blood cells [6]. Anemia can result in a reduced perceived health status (HS) or quality of life (QOL) [7, 8], and increased fatigue [9]. Also, vitamin D deficiency is reported to be related to HS [10] and fatigue [11, 12]. The current literature on postpartum micronutrient status focuses on lactating women and the impact of the amount of micronutrients secretion in breast milk on infant development [13]. So far, only little attention has been paid to the consequences of micronutrient depletion on maternal HS and fatigue during the postpartum period. Improved knowledge of postpartum micronutrient deficiencies and its association with maternal HS is important, in order to determine the need for supplementation. In this thesis, we examine anemia, iron, folic acid, vitamin B12, and vitamin D in association with HS and fatigue in postpartum women.

Postpartum health status and quality of life

Since health care is becoming more and more patient centered, patient-reported outcomes (PROs) become increasingly important. Frequently used aspects of PROs are QOL and perceived HS, which are multidimensional concepts that incorporate at least the physical, psychological, and social aspects of life [14]. These aspects are derived from the World Health Organization's (WHO) definition of health that is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [15]. QOL is defined by the WHOQOL group as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [16]. The difference between HS and QOL is that where HS refers to self-perceived physical, psychological and social *functioning*, QOL also incorporates the patients' *evaluation of functioning* with these aspects of life [14]. Both HS and QOL can be used to measure the perceived condition and to assess the effect of interventions [14]. Even though these terms are often used interchangeably, it is important to distinguish them from each other, as they may give different outcomes [17, 18]. In this thesis, we were interested in both QOL and HS in postpartum women (chapter 2). In addition,

we examined the association of postpartum micronutrient status and maternal HS and fatigue.

Postpartum micronutrient deficiency associated with health status and fatigue

Anemia can be caused by iron, folic acid or vitamin B12 deficiency [6]. In the current literature, anemia, whether or not caused by micronutrient deficiency, and vitamin D deficiency were found to be associated with impaired HS [7, 10] and increased fatigue [9, 11, 12]. Treatment of postpartum anemia is based on the assumption that fatigue will reduce and HS will improve, since fatigue is considered to be the major symptom of anemia [9]. An observational study of Jansen et al. found that the hemoglobin (Hb) level was correlated with physical HS and fatigue immediately postpartum, but disappeared one week postpartum [19]. As far as we know, there are no data comparing HS and fatigue among postpartum anemic and non-anemic women. In this thesis, we examined the difference in HS and fatigue between postpartum anemic and non-anemic women during the first five weeks postpartum (chapter 3).

Vitamin D deficiency was found to be associated with fatigue in the general population [11, 12] and with impaired HS in premenopausal women [10]. The prevalence of vitamin D deficiency and insufficiency during pregnancy ranges from 25 to 100%, depending on the country of residence [20]. At six to eight weeks postpartum, inadequate vitamin D levels were reported in 23% of Danish and 99.7% of Indian lactating women [21, 22]. Interestingly, the prevalence of vitamin D deficiency in bottle feeding postpartum women is unknown. Currently, international guidelines recommend supplementation of 10 – 15 micrograms (= 400 – 600 UI) vitamin D per day for pregnant and lactating women, in order to reduce the risk of vitamin D deficiency of the newborn [23, 24]. However, if vitamin D insufficiency in postpartum women is related to HS and fatigue, vitamin D supplementation might also be applied for all postpartum women independent of lactation. In this thesis, we studied the prevalence of vitamin D sufficiency and insufficiency in postpartum women, in relation to infant feeding method, HS and fatigue (chapter 4).

Postpartum anemia

Causes of postpartum anemia may include: hemodilution [8, 25], peripartum hemorrhage [25, 26], or deficiencies of micronutrients for erythropoiesis such as iron, folic acid [6, 25], and vitamin B12 deficiency. Only a minority of postpartum anemia is caused by vitamin B12 deficiency [25]. Nevertheless, low serum vitamin B12

levels are frequently found in postpartum women. It is known that serum vitamin B12 levels decrease during pregnancy, and recover spontaneously postpartum to preconceptional values [27, 28]. Despite the decrease of vitamin B12 to marginal or non-pregnant deficient values, there is no evidence of a true vitamin B12 deficiency. Homocysteine and methylmalonic acid levels, which are normally used to define vitamin B12 deficiency, were not significantly correlated with vitamin B12 deficiency both during pregnancy and postpartum [27, 28]. Therefore, the observed change is considered to be physiological and caused by a mechanism of redistribution of vitamin B12 bound to the proteins transcobalamin (holoTC) and haptocorrin (holoHC) [27, 29]. HoloTC is the metabolic active part of vitamin B12 available for tissue uptake [30] and has shown to be a more sensitive marker of early vitamin B12 changes compared with serum vitamin B12 in the general population [31, 32]. In this thesis, we examined the prevalence of vitamin B12 deficiency based on serum vitamin B12 and holoTC within 48 hours and at five weeks postpartum (chapter 5). Our hypothesis is that a shift occurs towards holoTC in women with insufficient available total vitamin B12. Therefore, the fraction of active vitamin B12 (holoTC/total vitamin B12) was compared between postpartum women with and without vitamin B12 deficiency (chapter 5).

Iron deficiency, ultimately resulting in iron deficiency anemia, is the most common form of malnutrition in the world and is highly prevalent in both developing and developed countries [33]. Because it is believed that the major causes of postpartum anemia include pre-existing iron deficiency and iron deficiency anemia in combination with excessive blood loss during delivery [3, 34], international guidelines recommend iron supplementation for the treatment of postpartum anemia [25, 34-36]. However, treatment guidelines of postpartum anemia are currently based on Hb level, without distinction between the etiologies of anemia [25, 34-36]. Yet, low Hb levels postpartum could be due to hemodilution [8, 25] or postpartum hemorrhage [26, 34]. Basing the treatment of anemia on Hb level alone, could lead to overtreatment in routine iron supplementation. Therefore, it is important to diagnose iron deficiency in anemic postpartum women. Iron deficiency is usually diagnosed by determination of a decreased level of serum ferritin [37, 38]. However, in the early postpartum period, serum ferritin can be false normal or false high, because of its prominent role in the acute phase response during parturition [36, 39]. For this reason, in this thesis, reticulocyte hemoglobin content (CHr) and mean corpuscular volume (MCV) were used to identify iron deficiency in postpartum anemic women (chapter 6), since these markers are not affected by the acute phase response [40].

In order to prevent iron deficiency anemia, the WHO recommends universal supplementation with iron and folic acid for 6 months during pregnancy [3, 33]. In areas with high prevalence (≥ 40%) of anemia in pregnant women, supplementation should be continued to the postpartum period to enable women to acquire adequate iron stores [3]. The Dutch guideline recommends treatment of anemia during pregnancy and the postpartum period with oral iron supplementation in iron deficiency anemia, and folic acid supplementation in folic acid deficiency anemia [41]. As previously mentioned, postpartum anemia is diagnosed based on Hb level alone [25, 35, 36]. In daily practice, both oral iron and folic acid are subscribed to treat postpartum anemia [42]. However, in the current literature it is unknown whether the addition of folic acid to oral iron supplementation is effective in the treatment of postpartum anemia. A randomized controlled trial in this thesis compared Hb level, HS, and fatigue after treatment of postpartum anemic women with oral iron supplementation or with oral iron and folic acid supplementation (chapter 7).

Aims of the thesis

Micronutrient deficiency is a common problem, which can worsen during pregnancy into the postpartum period. Deficiencies of the micronutrients iron, folic acid or vitamin B12 could result in anemia. Anemia and vitamin D deficiency were found to be associated with impaired HS and QOL [7, 8, 10], and increased fatigue [9, 11, 12]. However, maternal HS and fatigue in association with micronutrient deficiency is a neglected topic.

We intended to answer the following questions in this thesis:

- What are the HS and QOL in postpartum women and what factors contribute to this? (Chapter 2)
- What is the difference in HS and fatigue between anemic and non-anemic women during the first 5 weeks postpartum? (Chapter 3)
- What is the prevalence in vitamin D insufficiency in postpartum women, and is there an association with infant feeding method, HS, and fatigue? (Chapter 4)
- What is the course of vitamin B12 deficiency in the postpartum period? Does a shift occur towards holoTC in postpartum women with insufficient available total vitamin B12? (Chapter 5)
- Is it useful to measure MCV and CHr to identify truly iron deficient women with postpartum anemia? (Chapter 6)
- Is there an additional benefit in the treatment of postpartum anemia when folic acid is added to oral iron supplementation in order to improve Hb level and HS, and to reduce fatigue? (Chapter 7)

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Chapter 2

Health status and quality of life in postpartum women: a systematic review of associated factors

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Abstract

Since health care is becoming more and more patient centered, patient-reported outcomes such as quality of life (QOL) and health status (HS) are becoming increasingly important. The aim of this systematic review was to provide an overview of physical, psychological, and social domains of QOL and HS in postpartum women, and to assess which factors are associated with QOL and HS domains postpartum.

A computerized literature search was performed using the PubMed, PsycINFO, and Cochrane databases. Studies were selected if the three domains of QOL or HS were measured in a (sub)group of postpartum women, by using validated standardized questionnaires.

The methodological quality of the 66 included studies was examined by two independent reviewers.
All three domains of QOL were impaired in postpartum women with urinary incontinence, with even worse QOL in women with mixed urinary incontinence. Mental QOL was impaired in women with urge urinary incontinence after cesarean section. Social QOL was decreased in HIV-positive women. HS was impaired in all three domains in postpartum depressed women. Physical HS was impaired after cesarean section for at least two months postpartum. Additional supportive interventions from health care or social support were not associated with improved HS.

Urinary incontinence and being HIV-positive seemed to be associated with impaired QOL. Postpartum depression and a cesarean section seemed to be associated with impaired HS. Prospective longitudinal research is needed in order to draw valid conclusions regarding postpartum HS and QOL, and the predictive value of the associated factors.

Introduction

Worldwide, 255 women give birth to a child every minute [1]. The postpartum period, or puerperium, is considered to start one hour after delivery and is traditionally supposed to end six weeks after birth as it was believed that the body of the woman has then returned to the non-pregnant state [2]. However, a number of health conditions last even more than two years postpartum [3]. The postpartum period is characterized by several physical and mental health problems. The most common problems are urinary and fecal incontinence, infection, sexual problems, breast problems, anemia, wound problems, headache, backache, constipation, hemorrhoids, fatigue, depression, and anxiety [2-4]. These health problems can lead to sick leave and long-term sickness absence from work [5]. Since postpartum women have to cope with all these changes, their quality of life (QOL) and health status (HS) can be impacted [6].

QOL and HS are important categories of patient-reported outcomes (PROs), in which the patients perspective is key, and that can be used to assess the impact of current HS and to assess the efficiency of interventions [7]. The difference between these PROs is that where HS refers to self perceived physical, psychological and social *functioning*, QOL also incorporates patients' *evaluation of functioning*, i.e. (dis)satisfaction with these aspects of life [7]. Since health care is becoming more and more patient centered, the assessment of the patient's subjective experience is considered to be essential for informed clinical decision-making and health policy [8]. Therefore, research on QOL and HS in postpartum women is increasing, in which multiple contributing factors and interventions are examined.

The objective of this systematic review was to provide an overview of the core domains (physical, psychological, and social) of QOL and HS in postpartum women after the birth of a live infant, and to assess which factors are associated with QOL and HS domains postpartum.

Methods

Sources and selection criteria

A two-step literature search was conducted on 29 July 2014 using the PubMed, PsycINFO, and Cochrane databases. First, the following keywords and Boolean operators were used: (maternal OR women OR mothers) AND (postpartum OR postnatal OR puerperium) AND (health status OR quality of life). No limit was set with regard to publication date. The search was performed according to the guidelines of the Cochrane Collaboration [9]. Second, the reference lists of relevant articles were consulted and articles were added if they met the inclusion criteria.

All studies that met the following criteria were included: (1) QOL or HS was (part of) the outcome; (2) results included at least the physical, mental, and social domains of QOL or HS; (3) the study population included a (sub)group of postpartum women; (4) the article was a full report (no case report, editorial, poster text, letter or review) published in English, Dutch, or German; (5) HS or QOL were measured using standardized validated questionnaires; (6) studies were published in peer reviewed journals. Since QOL and HS should at least include the physical, mental and social domains, studies were excluded if they lacked one of these domains [10, 11]. Studies were also excluded if they only reported a total score for QOL and/or HS without reporting the scores of the different domains, to be sure that the three domains were measured.

Quality assessment

Each study was evaluated for quality and risk of bias using a standardized systematic review checklist of 18 predefined criteria by two reviewers independently (DW and JDV or DW and JP). The checklist was based on established criteria for systematic reviews and on established criteria for reviewing QOL studies [12-18].These criteria are presented in Table 1. One point was assigned to each item which met a criterion. If an item did not meet a particular criterion, was described insufficiently, or not at all, no point was assigned. As a result, the scores for each article can range from 0 to 18 points. Disagreement about the quality of studies was solved through open discussion. The quality scores of the included articles are presented in Table S1.

Table 1 Criteria for assessing the methodological quality of studies

Positive if with respect to	
QOL assessment	
A.	A description is given of QOL and/or HS by (i) describing at least the domains and/or (ii) indicating that QOL/HS reflects the subjective experience of the patient
B.	A reason is given for choosing a certain questionnaire
C.	A distinction is made between QOL and HS
Study population	
D.	The study describes its ethical approval (e.g. ethics committee or institutional review board, etc)
E.	A description is included of at least two socio-demographic variables (e.g. age, sex, employment status, education status, etc.)
F.	A description is present of at least two clinical variables (e.g. duration of symptoms, use of medication, etc)
G.	Inclusion and/or exclusion criteria are provided
H.	The study describes potential prognostic factors by using multivariate analysis or structural equation modeling
I.	Participation rates for patient groups are described and these rates are exceeding 75%
J.	Information is given about the non-responders versus responders
Study design	
K.	The study size is consisting of at least 50 patients (arbitrarily chosen)
L.	The collection of data is prospectively gathered
M.	The design is longitudinal (more than one year)
N.	The process of data collection is described (e.g. interview or self report, etc)
O.	The follow up period is at least 6 months
P.	The lost to follow-up is < 20%
Results	
Q.	The results are compared between two groups or more (e.g. health population, groups with different age) and/or results are compared with at least two time points (e.g. longitudinally or pre- versus post-treatment)
Outcome measures	
R.	A psychometrically sound QOL or HS questionnaire is used

Studies scoring ≥ 12 points were considered to be of "high quality", studies scoring between 9 and 12 points were considered to be of "moderate quality", and studies scoring < 9 points were considered to be of "low quality". This scoring system is based on previously published reviews regarding QOL and HS, and helps to weigh the impact of the results with the quality of the included studies [14-16, 19, 20]. Studies with higher scores, weigh more in processing the results. Therefore, if only one article displays a certain association, this does not mean that evidence for this association exists. When studies reported results of the same patient sample, only the highest quality study was included.

Data extraction and analysis

DW performed the data extraction and summarized the following variables in Tables S2a (QOL) and S2b (HS): study design, study size and population, intervention (if

appropriate), time of postpartum measurement, and results. When in doubt, JDV or JP were accessible for consultation.

Findings were considered consistent if ≥ 75% of the studies in which a particular factor was investigated showed the same direction of the association. We defined four levels of evidence which we used to describe the results: strong, moderate, weak, and inconclusive evidence (Table 2). This was based on previously published reviews regarding QOL and HS [14-16, 19, 20]. If less was published on a particular topic, the evidence was considered insufficient. The insufficient evidence was not processed in the results section of this review, but can be found the summary tables S2a and S2b. The results were presented by PRO (QOL or HS) and subcategorized in the physical, mental and social domains.

Table 2 Level of evidence

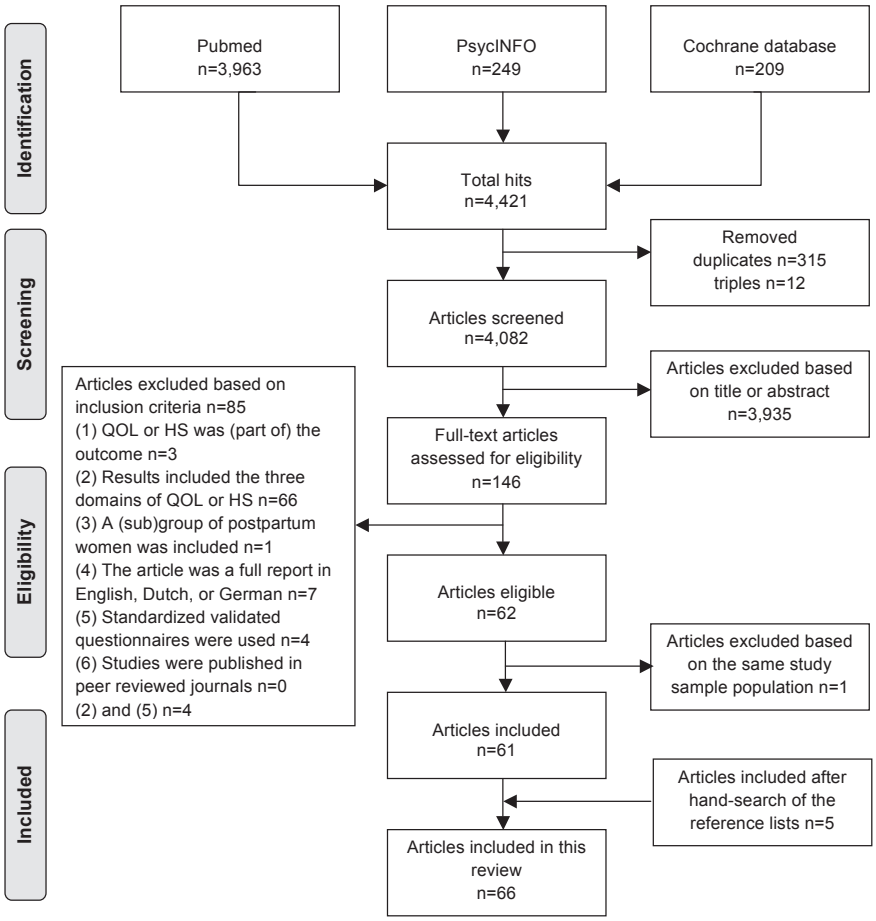
Strong	Consistent findings in at least two high-quality studies or consistent findings in one high-quality study and at least three moderate-quality studies
Moderate	Consistent findings in one high-quality study and at least one low-quality study or consistent findings in at least three moderate-quality studies
Weak	Consistent findings in two moderate-quality studies or consistent findings in at least three or more low-quality studies
Inconsistent	Inconsistent findings irrespective of study quality

Results

Study selection

The process of study selection is presented in Figure 1. The first literature search step identified 4,421 articles. After eliminating duplicates (n = 315) and triples (n = 12), 4,082 articles remained. The titles and abstracts of the 4,082 articles were screened and evaluated for eligibility by the first author (DW). The inclusion and exclusion criteria were applied to the abstracts, resulting in 3,935 excluded articles. If in doubt, the article was read in its entirety. Of the remaining 146 articles, one was not available in full text. This article was provided to us by the corresponding author [21]. After reading the 146 articles, 62 articles fulfilled the selection criteria in agreement with JDV. To decrease risk of bias in processing the results, one study was excluded because the results of the same patient sample were reported [22]. The hand search of the reference lists resulted in five additional articles [23-27]. A total of 66 articles were included in this review.

Figure 1 Process of study selection



Study characteristics

The included studies were conducted between 1996 and May 2014. Twenty-three studies claimed to measure QOL but measured HS. Their results were summarized in the HS table (Table S2b). Twenty-four studies measured QOL [6, 21, 28-49], 40 studies measured HS [23-27, 50-84], and two studies measured both [85, 86]. The studies were heterogeneous with regard to sample size, timing of first postpartum assessment, and interventions or factors examined. None of the studies used healthy fertile women as a comparison group.

Five validated HS questionnaires and 12 validated QOL questionnaires were used in the included studies (Table S3). The Medical Outcomes Study 36 Item Short Form Health Survey (SF-36) was most commonly used to measure HS (35 studies) and the World Health Organization Quality of Life Assessment-Bref (WHOQOL-Bref) was most commonly used to measure QOL (10 studies). The Incontinence Impact Questionnaire (IIQ) or Incontinence Impact Questionnaire short form (IIQ-7) was the most frequently used disease-specific questionnaire (five studies).

The quality scores ranged from 6 to 14 points (mean ± standard deviation: 10.7 ± 1.7). Twenty-three studies (35%) were considered to be of high quality, 35 studies (53%) were considered to be of moderate quality, and eight studies (12%) were considered to be of low quality. Methodological shortcomings mainly concerned the poor distinction made between QOL and HS (n = 6), the low number of longitudinal studies (n = 7), and often no information is given about the non-responders versus responders (n = 13).

Quality of life in postpartum women

Physical quality of life

Weak evidence was found for the lack of an association between mode of delivery and physical QOL in postpartum women, since there was no difference between scores after a cesarean section and vaginal delivery [40, 41]. Strong evidence was found for the lack of an association between physical QOL and the mode of delivery (vaginal delivery or cesarean section) in postpartum women with stress urinary incontinence [30, 33]. Weak evidence was found for an impairment in physical QOL in postpartum women with urinary incontinence, but these studies did not use a comparison group [32, 35, 86]. Also, weak evidence showed that mixed urinary incontinence in postpartum women was associated with worse physical QOL scores when compared to only stress- or urge urinary incontinence in these women [21, 86].

Mental quality of life

Moderate evidence was found for reduced mental QOL scores in postpartum women with urinary incontinence, without using a comparison group [25, 55, 70, 71]. Strong evidence was found for the lack of an association between mental QOL and mode of delivery in postpartum women with stress urinary incontinence [30, 33]. There were no differences in mental QOL scores after a vaginal delivery or cesarean section. Strong evidence was found for the association of mental QOL and mode of delivery in women with urge urine incontinence [30, 33]. Postpartum women with urge urine

incontinence after a cesarean section reported worse mental QOL when compared to women with urge urine incontinence after a vaginal delivery. Weak evidence showed that postpartum women with mixed urinary incontinence reported worse mental QOL scores when compared to postpartum women with only stress- or urge urinary incontinence [21, 86].

Inconsistent evidence exists with regard to mode of delivery and mental QOL postpartum. One study found no difference in mental QOL scores in postpartum women after a cesarean section and vaginal delivery [40]. Another study found worse mental QOL scores in postpartum women after a cesarean section compared to after a vaginal delivery, but this just reached significance ($p = 0.047$) [41].

Social quality of life

Without using a comparison group, weak evidence was found for reduced social QOL scores in postpartum women with urinary incontinence [32, 35, 86]. Strong evidence was found for the lack of an association between mode of delivery (vaginal delivery and cesarean section) and social QOL in postpartum women with stress urinary incontinence [30, 33]. Weak evidence showed that mixed urinary incontinence in postpartum women was associated with worse social QOL scores when compared to only stress- or urge urinary incontinence [21, 86]. Moderate evidence was found for the association of social QOL and the human immunodeficiency virus (HIV). HIV-positive postpartum women scored worse on social QOL compared with HIV-negative postpartum women [43, 44].

Inconsistent evidence was found with regard to mode of delivery and social QOL postpartum. One study found worse postpartum social QOL in women after a cesarean section compared to women after a vaginal delivery [41], but another study found no difference [40].

Health status in postpartum women

Physical health status

Strong evidence was found for the association of physical HS and mode of delivery. Postpartum women after a cesarean section reported worse physical HS compared to women after a vaginal delivery for at least two months postpartum [51, 53, 64, 65, 78]. Moderate evidence showed that depressed postpartum women scored significant worse on the SF-36 scales vitality and role limitations due to physical health compared

to normative means [25, 55]. Also, weak evidence showed that depressed postpartum women scored worse on the physical component summary of the SF-36 compared to postpartum women without depression [69-71]. Moderate evidence found no association of physical HS and additive supportive interventions from health care. Three randomized controlled trials found no improvement in any of the physical SF-36 scales after adding supportive interventions from health care [73-75].

Inconsistent evidence was found with regard to physical health change in healthy women from pregnancy to postpartum. Four studies found improvement of physical functioning [51, 52, 60, 61], but one found no difference [54]. Also, inconsistent evidence exists on pelvic muscle exercises for persistent pelvic pain in postpartum women and physical HS. Two randomized controlled trials compared the pelvic muscle exercises to standard care. One of these trials found no improvement of physical HS after exercise [27], but the other trial did find an improvement after exercise, even after two years of follow-up [76, 77].

Mental health status

Moderate evidence showed that depressed postpartum women scored worse on all SF-36 mental health scales compared to normative means [25, 55]. Also, weak evidence showed that women with postpartum depression scored worse on all SF-36 mental health scales, including the mental component summary, compared to women without postpartum depression [69-71]. Moderate evidence from three randomized controlled trials showed that postpartum mental HS was not influenced by additive supportive interventions from health care. None of the SF-36 mental scales improved [73-75].

Inconsistent evidence was found with regard to mental health change in healthy women from pregnancy to postpartum. Three studies found improvement of mental health [51, 54, 61], but two studies found no difference [52, 60]. Also, inconsistent evidence was found for the association of mode of delivery and mental HS. At six weeks postpartum, one study found worse mental health after an elective cesarean section compared with a vaginal delivery, but found no difference comparing an emergency cesarean section with a vaginal delivery [64]. Three studies found worse mental health after a cesarean section compared with a vaginal delivery at four to 38 weeks postpartum [55] between six to eight weeks postpartum [78], and at four months postpartum [65], Three studies found no difference in mental HS between 24 and 48 hours postpartum [53], between one and two weeks postpartum [53], at two months postpartum [65], and between 12

and 14 weeks postpartum [78]. Inconsistent evidence was found for the effect of pelvic muscle exercises in postpartum women with persistent pelvic pain on mental HS. One randomized controlled trial found no difference in mental HS after exercise compared to standard care [27]. Another randomized found an improvement of mental HS after exercise, even after two years of follow-up [76, 77]. For the association of abuse of postpartum women and mental HS, inconsistent evidence exists. One study found worse mental HS in abused postpartum women compared to non-abused postpartum women [67]. The abuse consisted of physical, psychological, or sexual abuse, but could also consist of a combination of abuses. Another study found only worse mental HS in postpartum women experiencing both psychological and physical abuse compared to non-abused postpartum women [68]. Women experiencing only psychological or physical abuse did not differ with regard to mental HS compared to non-abused women [68]. Furthermore, inconclusive evidence was found with regard to parity and mental HS. One study found that having a greater number of children was negatively related to mental health [24]. However, another study found no association between parity and mental health [55].

Social health status

Moderate evidence showed that postpartum depressed women scored worse on the SF-36 social functioning scale compared to normative means [25, 55]. Also, weak evidence showed that women with postpartum depression scored worse on the SF-36 social functioning scale compared to women without postpartum depression [69-71]. Moderate evidence showed that adding supportive interventions from health care was not associated with social HS in postpartum women. Three randomized controlled trials found no improvement on the SF-36 social functioning scale after adding supportive interventions from health care [73-75].

Inconclusive evidence was found with regard to social health change in healthy women from pregnancy to postpartum. One study found improvement of social health [51], two studies found impairment of social health [52, 54], and two studies found no difference [60, 61]. Inconclusive evidence exists on pelvic muscle exercises for persistent pelvic pain in postpartum women and social HS. An improvement of social HS was found in one randomized controlled trial [76], and in their follow-up study after two years [77]. Another randomized controlled trial found no difference in social HS comparing the pelvic muscle exercises to standard care [27]. Evidence on the association between abuse and postpartum social HS was also inconclusive. Social HS

was impaired in abused postpartum women compared to non-abused postpartum women in one study [67]. However, another study found that social HS was only impaired in postpartum women experiencing both psychological and physical abuse compared to non-abused postpartum women [68].

Discussion

All three QOL domains were impaired in postpartum women with urinary incontinence, with worse impairment in mixed urinary incontinence compared to stress and urge urinary incontinence. Impairment of mental QOL seemed to be associated with urge urinary incontinence after cesarean section. Social QOL seemed to be decreased in HIV-positive women. QOL seemed not to be associated with mode of delivery in postpartum women with stress urinary incontinence. HS seemed to be impaired in all three domains in postpartum depressed women. Physical HS seemed to be impaired after a cesarean section for at least two months postpartum. Additional supportive interventions from health care improved none of the HS domains.

In present review, urinary incontinence in postpartum women was found to be associated with impaired QOL in all three domains. This corresponds to a consensus in the literature that urinary incontinence affects QOL in women [87, 88]. Urinary incontinence was earlier found to affect physical and psychological wellbeing, but also socio-economical and sexual aspects of women [89, 90]. As in the current literature, mixed urinary incontinence was found to have a higher impact on QOL than stress or urge incontinence [90-92]. This probably has to do with the fact that these women experience coexisting symptoms of stress and urge urinary incontinence and have more severe urinary incontinence [91, 92].

After a cesarean section, urge urinary incontinence was associated with impaired mental QOL compared to women after a vaginal delivery. At the same time, the mode of delivery in postpartum women with stress urinary incontinence was not associated with QOL. Maybe, women after a cesarean section have different expectations than after a vaginal delivery, which can explain these results [33].

HIV-positivity was associated with impairment in social QOL in postpartum women. HIV patients have to cope with the fear of stigma and discrimination [93]. HIV-positive

women are particularly vulnerable to rejection and the loss of important familial and social relationships [94, 95].

All three domains of HS were impaired in women with postpartum depression compared to women without postpartum depression and to normative means. This corresponds to a number of symptoms associated with the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for postpartum depression, such as loss of energy or fatigue, depressed mood, and loss of interest or pleasure [96]. The impairment in social functioning fits the DSM criterion that these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning [96].

As expected, physical HS was impaired in women after a cesarean section. Physical recovery takes time after surgery, such as a cesarean section, and could be hindered by pain and reduced mobility [97].

The current review found no association of additional supportive interventions from health care with improved HS in all three domains. This corresponds to a systematic review examining the effect of additional social support and postpartum care on postpartum HS [98].

The strength of this review is that it includes all studies examining the core domains of QOL and HS in postpartum women as defined by the World Health Organization (WHO); physical, mental, and social domain [10, 11].

Some limitations of our review should be acknowledged. First, because the present review is a systematic review and not a meta-analysis, the quality of the included studies is the most important to weigh the impact of the results. The scoring system used is based on previously published reviews regarding QOL and HS [14-16, 19, 20]. Data were pooled by the quality of the included studies. Therefore, no statement can be made about the magnitude of the results. Secondly, a range of different questionnaires were used to measure QOL or HS. However, most HS studies used the SF-36 and most QOL studies used the WHOQOL-Bref or IIQ. Finally, publication bias can be present. However, the results on the different domains can differ, which makes it more likely that no publication bias is present.

In conclusion, urinary incontinence and being HIV-positive seemed to be associated with impaired QOL. Postpartum depression and a cesarean section seemed to be associated with impaired HS. Additional supportive interventions from health care were not associated with improved HS.
Prospective longitudinal research with healthy and demographic matched controls is needed in order to draw valid conclusions regarding postpartum HS and QOL, and the predictive value of the associated factors. In order to ensure comparability, all studies must use the same validated instruments.

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Chapter 3

Health status and fatigue of postpartum anemic women: a prospective cohort study

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Abstract

Objective: The incidence of postpartum anemia is high. Current therapy consists of iron supplementation or blood transfusions, based on the assumption that these treatments improve health status (HS) and reduce fatigue. The aim of this study was to compare HS and fatigue in postpartum women with and without anemia.

Study design: This prospective cohort study was performed in The Netherlands between April 2008 and August 2010 and involved 112 anemic (hemoglobin [Hb] < 10.5 g/dL) and 108 non-anemic (Hb ≥ 10.5 g/dL) women. The anemic women received oral iron supplementation. Within 48 hours and 5 weeks after delivery, HS was measured using the 36 item Short-Form Health Survey (SF-36) and fatigue was measured using the Checklist Individual Strength (CIS). ANOVA for repeated measures was used to compare HS and fatigue scores among groups and across time.

Results: After adjustment for confounding variables, there were no interaction effects in any of the HS and fatigue scores. SF-36 physical functioning ($p < 0.0001$), social functioning ($p = 0.025$) mental health ($p = 0.043$), vitality ($p = 0.001$), bodily pain ($p = 0.01$), physical component summary ($p < 0.0001$), mental component summary ($p = 0.02$), and total scores ($p < 0.0001$), and the CIS subscales subjective fatigue ($p < 0.0001$), motivation ($p < 0.0001$), activity ($p = 0.005$), and total scores ($p < 0.0001$) improved across time. No significant differences between the anemic and non-anemic group were observed. Regression analyses showed no association of anemia and the amount of blood loss with any of the SF-36 and CIS scales at both time points, but did show that cesarean section was associated with lower physical HS on both time points.

Conclusion: HS and fatigue were not different among women with and without postpartum anemia.

Introduction

Postpartum anemia is a worldwide problem with a prevalence ranging from 22% to 50% in developed countries and from 50% to 80% in developing countries [1]. Major causes of postpartum anemia include pre-existing iron deficiency and iron deficiency anemia (IDA) in combination with excessive blood loss during delivery [2]. Ferritin, a marker used to diagnose IDA, is not useful in the early postpartum period because of its prominent role in the acute phase response during parturition [3,4]. Therefore, the definition and indication for the treatment of postpartum anemia are based on hemoglobin (Hb) level [3,5,6].

Fatigue is considered the major symptom of anemia [7]. This type of fatigue is not an isolated physical symptom, but involves lethargy, decreased mental alertness, physical weakness, and poor concentration [8]. Uncorrected IDA may have a negative impact on maternal cognition, mood and behavior, and could thereby alter mother-child interactions [9,10]. Therefore, health status (HS), a multidimensional concept that incorporates the self-perceived functioning of physical, psychological, and social aspects of life [11], is regarded as reduced in women with postpartum anemia [1].

To date, few studies have compared HS and fatigue between women with and without postpartum anemia. An observational study examined the natural course of HS and fatigue during the first 6 postpartum weeks in relation to mode of delivery [12]. In addition to physical HS being significantly poorer after a cesarean section than after a vaginal delivery, Hb level was found to be negatively correlated with physical HS and fatigue immediately postpartum. This correlation had disappeared 1 week postpartum. If necessary, women were treated postpartum with oral iron and folic acid. To our knowledge, however, HS and fatigue scores have not been compared in women with and without postpartum anemia.

In the present study, we examined differences in HS and fatigue between anemic and non-anemic women during the first 5 weeks postpartum. We also investigated changes in HS and fatigue over time. Furthermore, regression analyses were performed to assess the effect of anemia, the amount of blood loss, and mode of delivery on HS and fatigue.

Materials and methods

The current prospective cohort study was performed between April 2008 and August 2010 at a large teaching hospital in Tilburg, in the southern part of The Netherlands. The threshold for the definition of anemia in the early postpartum period varies between < 11.0 g/dL and < 10.0 g/dL [1,3]. Anemia in the current study was defined according to the Dutch guidelines as Hb concentration < 10.5 g/dL [5]. The anemic women were part of a randomized controlled trial that showed no between-group differences in Hb, HS, and fatigue after receiving oral iron supplementation with and without folic acid [13]. Non-anemic women (Hb ≥ 10.5 g/dL) received no treatment and were followed prospectively during the study.

Women were eligible for inclusion if they were ≥ 18 years old, thoroughly understood the Dutch language, and had indications for Hb determination within 48 hours after delivery, including estimated blood loss > 500 ml, delivery by cesarean section, manual removal of the placenta, and clinical symptoms of anemia.

Women were excluded if: their Hb was < 6.4 g/dL (because the hospital protocol indicates the need for packed red cell transfusion); they were addicted to alcohol or drugs; they had hematological diseases such as hemoglobinopathies, sickle cell disease, thalassemia, and Hemolysis Elevated Liver enzymes and Low Platelets syndrome (HELLP); they had vitamin B12 deficiency (serum vitamin B12 < 100 nmol/L and holotranscobalamine < 20 pmol/L); they had chronic inflammatory disease; they were being treated with methotrexate; or they had contra-indications to treatment with folic acid or ferrous fumarate.

The study protocol was approved by the local ethics committee (file number NL21797.028.08). All women received oral and written information about the study, and provided oral and written informed consent.

Maternal venous blood was collected and questionnaires to assess HS and fatigue were completed within 48 hours postpartum (T0) and again at the outpatient clinic 5 weeks after delivery (T5). The outcome measures were HS and fatigue improvement among groups and across time.

Hb was analyzed using an Advia 2120i automated cell counter (Siemens Healthcare Diagnostics, Breda, The Netherlands). Hb, measured as mmol/L, was converted to g/dL by multiplying by 1.6115.

HS was measured using the self-reported standardized 36 item Short-Form Health Survey (SF-36), a generic questionnaire that was chosen because it covers all HS domains and is often used in determining HS in postpartum women, allowing good comparability among studies. The 36 items are organized into eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Each item has a scoring range from 0 to 100, with higher scores representing better levels of functioning [14]. In addition, the SF-36 provides a physical component summary (PCS) and a mental component summary (MCS). The SF-36 has demonstrated good psychometric properties in postpartum women [15].

Fatigue was measured using the Checklist Individual Strength (CIS), a multidimensional scale that quantifies subjective fatigue and related behavioral aspects [16]. This questionnaire was chosen because fatigue is a symptom of anemia. The 20 items cover four dimensions: subjective experience of fatigue, reduced concentration, reduced motivation, and reduced physical activity level. Each item has a scoring range from 1 to 7, with higher scores indicating greater fatigue. The CIS has been shown reliable and valid in patients with chronic fatigue syndrome, as well as in healthy populations [17].

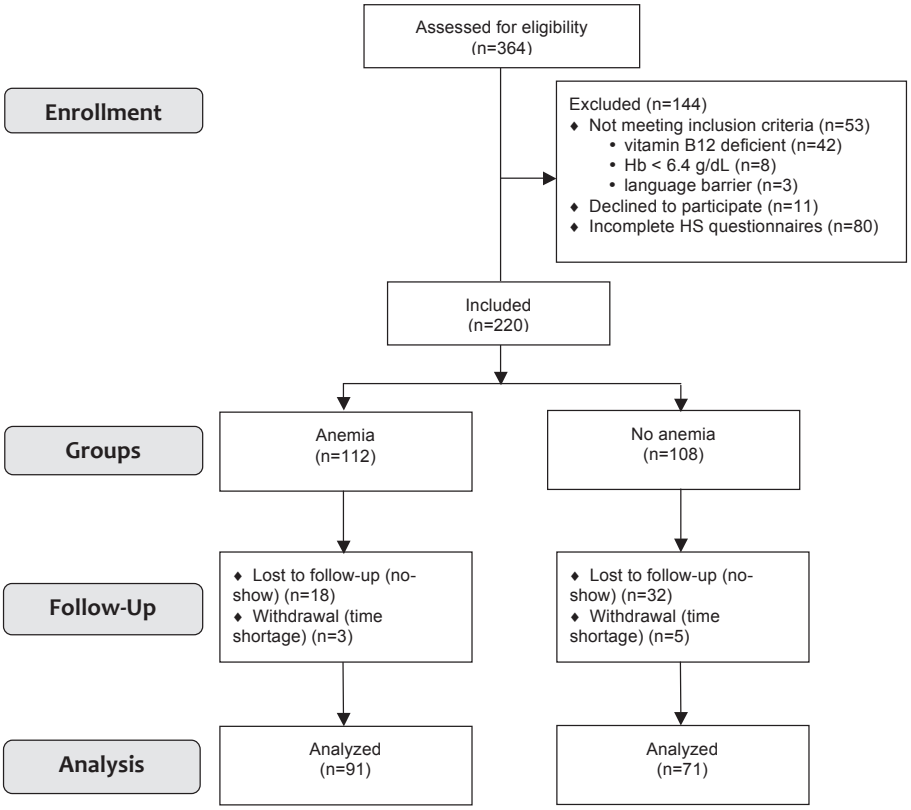
Statistical analyses were performed using SPSS 15.0. Baseline differences between the anemic and non-anemic women were assessed with independent sample T-tests, Mann-Whitney U tests or Chi-square tests. ANOVA for repeated measures were used to compare HS and fatigue scores among groups and across time. We corrected for the number of tests using the Bonferroni rule. Potential baseline differences and mode of delivery (vaginal/cesarean section) were entered as covariates, since cesarean section has been shown to affect physical HS [12]. We report both the unadjusted and adjusted results, to show the impact of these covariates. To make a more comprehensive assessment of the effect of anemia, the amount of blood loss, and mode of delivery on HS and fatigue, linear regressions (method: enter) were performed with the SF-36 and CIS subscales as dependent variables. Results are reported as the mean $\pm$ standard deviation (SD), mean $\pm$ standard error of the mean (SEM), or percentage (%), as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

Of the 364 women screened, 53 did not meet the inclusion criteria, including 42 with vitamin B12 deficiency, eight with Hb < 6.4 g/dL, and three due to a language barrier. Eleven women declined to participate. Eighty women did not complete the baseline HS questionnaires for unknown reasons and were therefore excluded.

A total of 220 women were included in the study, including 112 with anemia and 108 without anemia. A total of 50 participants were lost to follow-up after repeatedly not showing up for follow-up appointments. Eight withdrew before the follow-up appointment, mostly because of a lack of time. Thus, 91 anemic women and 71 non-anemic women were analyzed (Figure 1).

Figure 1 Flow of participants through the study



The demographic and clinical characteristics of the participants at baseline are shown in Table 1. The method of delivery differed significantly among the groups, with cesarean sections performed in 37.5% of the women with anemia and 71.3% of non-anemic women ($p < 0.013$). As expected, blood loss was significantly greater in anemic than in non-anemic women ($p < 0.0001$).

Table 1 Patient demographic and clinical characteristics at baseline (T0)

	Anemia (n=112)	No anemia (n=108)
Age at entry (years)	30.6 ± 4.7	31.4 ± 4.0
BMI before pregnancy (kg/m²)	25.2 ± 5.4	25.4 ± 5.6
Twin pregnancies	4 (3.6)	1 (0.9)
Ethnicity		
Caucasian	97 (86.6)	97 (89.9)
Turkish	5 (4.5)	7 (6.5)
African	5 (4.5)	2 (1.9)
Asian	3 (2.7)	0 (0.0)
South American	2 (1.8)	2 (1.9)
Highest education		
Lower	6 (5.6)	1 (1.0)
Medium	56 (52.3)	50 (47.6)
High	45 (42.1)	54 (51.4)
Smoking	15 (13.5)	7 (6.5)
Multivitamin use	45 (40.2)	54 (50.0)
Parity at baseline	1.5 ± 0.8	1.6 ± 0.7
Gestational age at delivery (weeks)	40.0 ± 1.5	39.7 ± 1.4
Delivery method [a]		
Vaginal	70 (62.5)	31 (28.7)
Cesarean section	42 (37.5)	77 (71.3)
Elective cesarean section	12 (28.6)	43 (55.8)
Emergency cesarean section	30 (71.4)	34 (44.2)
Estimated blood loss (ml) [b]	824 ± 416	505 ± 280
Infant feeding		
Breastfeeding	70 (62.5)	75 (69.4)
Bottle (formula) feeding	42 (37.5)	33 (30.6)

Numbers are mean ± SD or number (percentage).
BMI = Body Mass Index (calculated as weight in kilograms divided by the square of height in meters).
[a] Chi square: $p = 0.013$ between vaginal delivery and cesarean section, $p < 0.0001$ between vaginal delivery, elective cesarean section, and emergency cesarean section.
[b] Mann-Whitney U test: $p < 0.0001$.
Note: There were no significant differences between anemia versus non-anemia on the other variables.

Analysis of results on the SF-36 and CIS showed that, without adjusting for baseline differences (including delivery method), there were no interaction effects (Table 2). However, an effect of time was observed with regard to the SF-36 subscales physical functioning, social functioning, role physical, mental health, vitality, bodily pain, PCS, MCS, and total scores ($p < 0.0001$) and the CIS subscales subjective fatigue, motivation, and activity, and total scores ($p < 0.0001$). All scores improved. Also, a group effect for the SF-36 physical functioning scale ($p = 0.008$) and PCS ($p = 0.046$) was found. The anemic group scored higher compared with the non-anemic group.

Table 2 Health status and fatigue by group at baseline (T0) and at 5 weeks postpartum (T5) [a]

	Anemia		No anemia	
	T0	T5	T0	T5
SF-36				
Physical functioning	41.5 ± 3.5	82.0 ± 1.9	30.0 ± 4.0	75.9 ± 2.2
Social functioning	67.7 ± 2.8	85.0 ± 2.2	63.8 ± 3.2	78.2 ± 2.5
Role physical	34.4 ± 4.0	69.4 ± 4.4	32.2 ± 4.5	55.4 ± 5.0
Role emotional	85.4 ± 3.5	91.4 ± 3.9	81.9 ± 4.0	89.2 ± 4.5
Mental health	78.9 ± 1.6	86.3 ± 1.3	76.8 ± 1.8	84.9 ± 1.5
Vitality	54.7 ± 2.1	66.1 ± 2.6	55.6 ± 2.4	65.4 ± 3.0
Bodily pain	60.2 ± 3.1	84.2 ± 2.1	55.8 ± 3.6	80.8 ± 2.4
General health	80.1 ± 1.5	79.9 ± 1.7	78.4 ± 1.7	76.5 ± 1.9
Health change	44.8 ± 2.1	46.4 ± 2.0	46.8 ± 2.4	44.4 ± 2.3
PCS	53.9 ± 2.3	78.9 ± 2.0	49.4 ± 2.6	72.7 ± 2.3
MCS	71.5 ± 1.8	82.7 ± 1.9	69.4 ± 2.1	79.4 ± 2.1
Total	60.8 ± 1.7	76.9 ± 1.6	57.8 ± 1.9	72.7 ± 1.8
CIS				
Subjective fatigue	35.2 ± 1.3	26.2 ± 1.2	34.8 ± 1.5	29.0 ± 1.3
Reduced motivation	13.1 ± 0.6	8.6 ± 0.4	13.3 ± 0.7	9.9 ± 0.5
Reduced activity	11.8 ± 0.6	8.1 ± 0.5	12.3 ± 0.6	9.3 ± 0.5
Reduced concentration	15.0 ± 0.8	13.4 ± 0.8	15.4 ± 0.9	14.6 ± 0.9
Total	74.8 ± 2.7	56.4 ± 2.3	75.0 ± 3.1	62.8 ± 2.6

Numbers are mean ± SEM

SF-36 = 36 item short-form health survey, PCS = Physical component summary, MCS = Mental component summary, CIS = Checklist individual strength.

[a] Repeated measures ANOVA, without adjustments for baseline differences (mode of delivery and estimated blood loss)

After adjustment for baseline differences, including delivery method, there was also no interaction effect (Table 3). However, there was an effect of time for the SF-36 subscales physical functioning ($p < 0.0001$), social functioning ($p = 0.025$), role physical ($p = 0.002$), mental health ($p = 0.043$), vitality ($p = 0.001$), bodily pain (p

= 0.01), PCS (p < 0.0001), MCS (p = 0.02), and total scores (p < 0.0001), and the CIS subscales subjective fatigue (p < 0.0001), motivation (p < 0.0001), activity (p = 0.005), and total scores (p < 0.0001). All scores improved. On average, there were no significant differences between the anemic and non-anemic group.

Table 3 Adjusted health status and fatigue by group at baseline (T0) and at 5 weeks postpartum (T5) [a]

	Anemia		No anemia	
	T0	T5	T0	T5
SF-36				
Physical functioning	36.8 ± 3.5	79.4 ± 1.9	36.8 ± 4.0	79.2 ± 2.2
Social functioning	65.8 ± 2.9	84.0 ± 2.3	67.5 ± 3.4	79.3 ± 2.7
Role physical	32.8 ± 4.3	66.1 ± 4.6	35.2 ± 4.9	59.4 ± 5.3
Role emotional	85.9 ± 3.7	93.6 ± 4.2	80.5 ± 4.3	85.9 ± 4.8
Mental health	79.2 ± 1.7	87.0 ± 1.4	76.1 ± 2.0	84.1 ± 1.6
Vitality	54.7 ± 2.2	66.0 ± 2.8	56.0 ± 2.6	65.8 ± 3.2
Bodily pain	58.4 ± 3.3	81.9 ± 2.2	58.7 ± 3.9	83.6 ± 2.5
General health	79.6 ± 1.6	79.7 ± 1.8	79.1 ± 1.8	76.8 ± 2.0
Health change	44.4 ± 2.3	45.5 ± 2.2	48.2 ± 2.6	45.7 ± 2.5
PCS	51.9 ± 2.3	76.9 ± 2.1	52.5 ± 2.7	75.1 ± 2.4
MCS	71.3 ± 2.0	83.1 ± 2.0	69.8 ± 2.2	78.7 ± 2.3
Total	59.8 ± 1.8	76.1 ± 1.7	59.6 ± 2.1	73.6 ± 2.0
CIS				
Subjective fatigue	35.3 ± 1.4	26.3 ± 1.3	34.6 ± 1.6	28.9 ± 1.5
Reduced motivation	13.0 ± 0.7	8.7 ± 0.5	13.3 ± 0.8	9.8 ± 0.5
Reduced activity	12.0 ± 0.6	8.4 ± 0.5	12.2 ± 0.7	9.0 ± 0.6
Reduced concentration	14.8 ± 0.8	13.2 ± 0.9	15.4 ± 1.0	14.7 ± 1.0
Total	74.8 ± 2.9	56.6 ± 2.5	74.8 ± 3.3	62.5 ± 2.9

Numbers are mean ± SEM
SF-36 = 36 item short-form health survey, PCS = Physical component summary, MCS = Mental component summary, CIS = Checklist individual strength.
[a] Repeated measures ANOVA, adjusted for baseline differences (mode of delivery and estimated blood loss)

Linear regression analysis showed no association of anemia and the amount of blood loss with any of the SF-36 and CIS scales at both time points. Mode of delivery was associated with scores on the SF-36 scales physical functioning (ß = -0.29; p < 0.0001), social functioning (ß = -0.19; p = 0.027), bodily pain (ß = -0.19; p = 0.023), and PCS (ß = -0.23; p = 0.007) on T0. On T5, mode of delivery was associated with scores on the SF-36 scales physical functioning (ß = -0.43; p < 0.0001), role physical (ß = -0.24; p = 0.017), bodily pain (ß = -0.27; p = 0.008), and PCS (ß = -0.32; p = 0.002), and on the CIS scale reduced activity (ß = 0.31; p = 0.002). Women after cesarean section scored worse compared with women after a vaginal delivery. The explained variance (R^2) of

these significant variables ranged from 4.7% (SF-36 social functioning T0) to 17.4% (SF-36 physical functioning on T5).

Discussion

This prospective cohort study assessing postpartum HS and fatigue found no differences among groups of women with and without postpartum anemia adjusting for baseline differences in mode of delivery and the amount of blood loss. HS and fatigue scores significantly improved over time in all women.

Cesarean section was significantly more common in women without than with postpartum anemia, a difference that may explain the significant differences in physical functioning and PCS scores between these two groups before adjustment, since cesarean section is known to affect physical HS [12]. The anemic group more frequently delivered vaginally, with increased of blood loss, than the non-anemic group. By contrast, a previous study found that blood loss was greater in women who underwent cesarean section than those who delivered vaginally, although postpartum Hb levels did not differ significantly [18].

To our knowledge, this is the first study to compare all domains of HS and fatigue (physical, mental, and social functioning) in postpartum women with and without anemia. In contrast to previous findings, we observed no association between anemia and fatigue conceptions [7]. In agreement with an earlier study, we found that HS and fatigue scores improved over time in all groups and were not associated with Hb level [12].

A limitation of the present study was the selection bias. Hb and iron status was only determined if indicated. Since all women who underwent a cesarean section were subjected to routine blood analysis, 54% of the enrolled women delivered by cesarean section. We therefore adjusted for mode of delivery in our analyses. Based on the time required for erythroblast maturation, we expected that improvements in Hb concentrations and any differences in HS and fatigue scores among the groups would have been observed after 5 weeks [19]. Others have shown, however, that the average periods required to reach full recovery on physical HS scales were 3 weeks after vaginal delivery, 6 weeks after elective cesarean section, and more than 6

weeks after emergency cesarean section [12]. We performed a subgroup analysis to determine the effect of elective and emergency cesarean section on HS and fatigue and found no differences in any of the HS and fatigue scores between the groups (data not shown). Another limitation of this paper is that there is no blood measurement before delivery, since prepartum anemia combined with acute bleeding anemia due to blood losses at delivery are the major causes of postpartum anemia [1]. In The Netherlands, blood examination is regularly performed during pregnancy, and not routinely when women are admitted to the hospital for delivery. In accordance with international guidelines, iron treatment is based on Hb measurement at 48 hours postpartum [1,3]. Since prepartum Hb was lacking, anemic postpartum women might have been anemic before delivery. It is known that chronically anemic women get used to decreased energy levels; this could explain why no differences were found in HS and fatigue scores between anemic and non-anemic postpartum women. Future research should examine the effect of acute and chronic anemia postpartum on HS and fatigue.

Most studies on postpartum anemia have focused on hematological outcomes after iron supplementation, with many showing that iron had a positive effect on maternal iron status [6]. Our results, however, suggest that iron supplementation may not be necessary in the treatment of postpartum anemia. Since HS and fatigue did not differ among the groups, iron supplementation may only worsen HS because of its known side effects. A prospective longitudinal study is needed to determine the relationships between severity of postpartum anemia and maternal morbidity, HS, and fatigue in women who do and do not receive iron supplementation.

In conclusion, postpartum women with anemia did not show a greater improvement in HS and fatigue when compared with non-anemic women during the first 5 weeks postpartum. All women showed significant improvements in HS and fatigue over time.

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Chapter 4

The high prevalence of vitamin D insufficiency in postpartum women is not related to infant feeding method, health status and fatigue.

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Submitted

Abstract

Purpose: Vitamin D deficiency is a worldwide health problem that affects musculoskeletal health, acute and chronic diseases, and even fatigue. Inadequate vitamin D levels are highly prevalent in postpartum lactating women, who are advised to use vitamin D supplementation. The aim of this study was to assess the prevalence of insufficient vitamin D levels in postpartum women in relation to infant feeding method, and to compare health status (HS) and fatigue between vitamin D sufficient and insufficient postpartum women with regard to infant feeding method.

Methods: This cross-sectional observational study included 113 Dutch postpartum women with persistent breast or bottle feeding at 5 weeks postpartum. Vitamin D sufficiency was defined according to international guidelines as 25-OH-vitamin D ≥ 50 nmol/L. HS and fatigue were measured using the 36 item Short-Form Health Survey (SF-36), and the Checklist Individual Strength (CIS).

Results: Insufficient vitamin D levels were found in 57% of the breastfeeding women, and 64% of the bottle feeding women ($p = 0.46$). Scores on the mental health scale (SF-36) were significantly worse in vitamin D insufficient compared with sufficient breastfeeding women ($p = 0.034$). Among the bottle feeding groups, social functioning (SF-36) was significantly worse in the sufficient vitamin D group compared with the vitamin D insufficient group ($p = 0.047$). Linear regression analysis showed no association of infant feeding method with vitamin D concentration (ß = 0.00; $p = 1.00$). Summer (ß = 0.72; $p < 0.0001$) and fall (ß = 0.24; $p = 0.011$) were significantly associated with vitamin D concentration. Vitamin supplementation (ß = 0.27; $p < 0.0001$) and Caucasian ethnicity (ß = 0.18; $p = 0.015$) were also significantly associated with vitamin D concentration.

Conclusion: Postpartum vitamin D insufficiency was as frequent in lactating women as in women who bottle-fed their infant. HS and fatigue were not associated with insufficient vitamin D levels in postpartum women. In order to ensure good bone health, the international recommendation for supplementation of 10–15 micrograms vitamin D per day should include all postpartum women.

Introduction

Vitamin D deficiency has been recognized to be a worldwide health problem that affects not only musculoskeletal health, but also a wide range of acute and chronic diseases such as type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity, allergy, and even fatigue [1-4]. Impaired health status (HS) was also found to be associated with insufficient vitamin D levels in premenopausal women [5].

Vitamin D is a fat-soluble prohormone produced endogenously in the skin from sun exposure (66%) or obtained from food sources such as fatty fish, eggs, fortified milk, and cod liver oil or vitamin D supplements [1]. Vitamin D is hydroxylated in the liver to form the major circulating metabolite 25-hydroxyvitamin D (25-OH-vitamin D), which is used to determine a patient's vitamin D status [1]. Vitamin D levels decrease significantly during late pregnancy and even more in the postpartum lactating period [6, 7]. Inadequate vitamin D levels were reported in 23% of Danish and 99.7% of Indian lactating women at six to eight weeks postpartum [6, 8]. Low maternal vitamin D levels during pregnancy were found to be associated with an increased risk of preeclampsia, gestational diabetes mellitus, preterm birth, small for gestational age, and antenatal and postpartum depression [9-13]. Therefore, international guidelines recommend supplementation of 10–15 micrograms (= 400–600 UI) vitamin D per day for pregnant and lactating women [14, 15]. No recommendation exists for postpartum women who bottle feed their infants.

To date, comparative research on vitamin D status between breastfeeding and bottle feeding postpartum women is lacking. Because vitamin D deficiency has a high prevalence in lactating women, it is important to know if fatigue and HS is diminished in this group of women. HS is a multidimensional concept that reflects physical, mental and social functioning and can be assessed by HS measures [16]. The aim of the present study was to assess the prevalence of insufficient vitamin D levels in postpartum women in relation to infant feeding method, and to compare HS and fatigue between vitamin D sufficient and insufficient postpartum women with regard to infant feeding method. Linear regression analyses were performed to make a more comprehensive assessment of the effect of infant feeding method, season, ethnicity, and vitamin supplementation on postpartum vitamin D concentration.

Methods

The present cross-sectional study was conducted between April 2008 and August 2010 at the Department of Obstetrics and Gynecology, TweeSteden Hospital Tilburg, in the southern part of the Netherlands. Approval was obtained from the local ethic committee (file number NL21797.028.08). All women received verbal and written information about the study, and provided verbal and written informed consent.

Women were eligible for inclusion if they were 18 years or older, thoroughly understood the Dutch language, and had indications for hemoglobin (Hb) determination within 48 hours after delivery. Indications included estimated blood loss over 500 mL, delivery by cesarean section, manual removal of the placenta, and clinical symptoms of anemia. Women were excluded for the following reasons: Hb less than 6.4 g/dL (because the hospital protocol indicates the need for packed cell transfusion); addiction to alcohol or drugs; hematological disease; vitamin B12 deficiency (serum vitamin B12 < 100 nmol/l and holotranscobalamin < 20 pmol/l).

Maternal venous blood was collected and questionnaires assessing HS and fatigue were completed at the outpatient clinic at 5 weeks postpartum. Women were divided in two groups; those with persistent breastfeeding, and those with persistent bottle feeding during the first 5 weeks postpartum. Vitamin D sufficiency was defined according to international guidelines as 25-OH-vitamin D ≥ 50 nmol/L [6, 14, 17].

Venous blood samples were obtained in the non-fasting state. Serum was immediately separated and stored at – 80 °C. Serum 25-OH-vitamin D was measured by chemiluminescence immunoassay (CLIA) using a Liaison analyzer (Diasorin, Saluggia, Italy). The coefficient of variation of control material was 2.5 % (target value 50.9 nmol/L). To convert values from nmol/L to µg/L, multiply by 0.400641; to convert values from µg/L to nmol/L, multiply by 2.496.

HS was measured using the self-reported standardized 36-item Short-Form Health Survey (SF-36). The measure has eight scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) that form a physical component summary (PCS) and a mental component summary (MCS) [18]. The SF-36 has demonstrated good psychometric properties in postpartum women [19].

Fatigue was measured using the Checklist Individual Strength (CIS), a multidimensional scale that quantifies subjective fatigue and related behavioral aspects [20]. The 20-items cover four dimensions: subjective experience of fatigue, reduced concentration, reduced motivation, and reduced physical activity level. The CIS has been shown reliable and valid in patients with chronic fatigue syndrome, as well as in healthy populations [21].

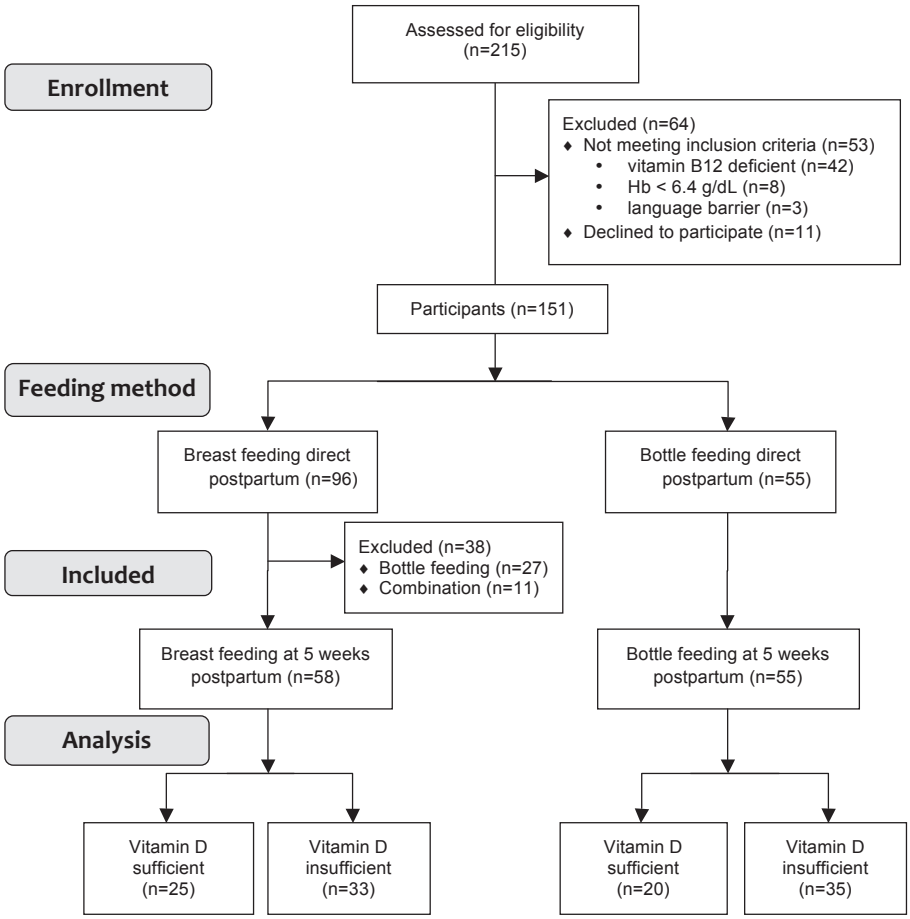
Statistical analysis

Statistical analyses were performed using SPSS 15.0. Continuous variables at baseline were compared by independent sample T-tests and nominal variables by Chi-square tests. Analyses of Covariance (ANCOVA) were used to compare HS and fatigue scores between sufficient and insufficient vitamin D level by infant feeding method. Potential baseline differences were entered as covariates. Linear regression analysis (method: enter) was performed to make a more comprehensive assessment of the effect of infant feeding method (breastfeeding or bottle feeding), season of inclusion (winter, spring, summer, and fall), ethnicity (Caucasian or not), and vitamin supplementation (yes or no) on postpartum vitamin D concentration. To assess the effect of season on vitamin D concentration, winter was chosen as reference group. All results are reported as mean $\pm$ standard deviation, mean (95% confidence interval), or number (percentage). A p-value of < 0.05 was considered statistically significant.

Results

A total of 113 women were included in this study; 58 women with persistent breastfeeding, and 55 women with persistent bottle feeding at 5 weeks postpartum. Insufficient vitamin D levels were found in 33 of the breastfeeding women, and 35 of the bottle feeding women (57% respectively 64%, p = 0.46) (Figure 1).

Figure 1 Flow of participants through the study



The demographic and clinical characteristics among the groups are shown in Table 1. There was a significant difference in age (p = 0.042) and distribution within included season (p < 0.0001) between the breastfeeding groups, and a significant difference in highest education (p = 0.006), vitamin use (p = 0.039), and distribution within included season (p = 0.01) between the bottle feeding groups.

Table 1 Demographic and clinical characteristics [a]

Characteristics	Breastfeeding		Bottle feeding	
	Sufficient (n=25)	Insufficient (n=33)	Sufficient (n=20)	Insufficient (n=35)
Age (years) [b]	31.2 ± 3.6	30.9 ± 5.2	30.2 ± 3.9	31.2 ± 4.4
BMI	25.1 ± 3.3	27.7 ± 5.8	26.6 ± 4.6	27.3 ± 5.4
Parity at baseline	1.5 ± 0.7	1.6 ± 0.9	1.5 ± 0.8	1.6 ± 0.7
Gestational age at delivery (weeks)	40.0 ± 1.4	39.7 ± 1.4	40.1 ± 1.3	39.7 ± 1.6
Caucasian ethnicity	23 (92)	24 (73)	20 (100)	32 (91.4)
Highest education [c]				
Lower	1 (4)	1 (3)	0 (0)	2 (6)
Medium	9 (36)	15 (47)	17 (85)	13 (41)
High	15 (60)	16 (50)	3 (15)	17 (53)
Vitamin use [d]				
No	8 (32)	16 (50)	10 (50)	27 (77)
Multivitamins or vitamin D	17 (68)	16 (50)	10 (50)	8 (23)
Delivery method				
Vaginal	9 (36)	17 (51.5)	12 (60)	14 (40)
Cesarean	16 (64)	16 (48.5)	8 (40)	21 (60)
Season [e,f]				
Spring	1 (4.0)	10 (30.3)	6 (30.0)	14 (40.0)
Summer	18 (72.0)	6 (18.2)	10 (50.0)	4 (11.4)
Autumn	6 (24.0)	9 (27.3)	2 (10.0)	4 (11.4)
Winter	0 (0.0)	8 (24.2)	2 (10.0)	13 (37.2)
Hemoglobin (g/dL)	12.9 ± 0.7	12.6 ± 0.9	12.6 ± 0.9	12.1 ± 1.2
Sleeping hours per night last week	6.3 ± 0.9	6.1 ± 1.3	6.2 ± 1.1	6.0 ± 1.7

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

[a] Values are given as mean ± SD or number (percentage)

[b] Independent T-test p = 0.042 between insufficient en sufficient groups of breastfeeding women

[c] Chi-square p = 0.006 between insufficient and sufficient groups of bottle feeding women

[d] Chi-square p = 0.039 between insufficient and sufficient groups of bottle feeding women

[e] Chi-square p < 0.0001 between insufficient and sufficient groups of breastfeeding women

[f] Chi-square p = 0.010 between insufficient and sufficient groups of bottle feeding women

Note: There were no significant differences between the other variables.

There were no significant differences on the HS and fatigue scales between the women with and without sufficient vitamin D levels in the breastfeeding women (Table 2). Among the bottle feeding groups, general health (SF-36) was significantly worse in the insufficient vitamin D group (p = 0.035, Table 3). Other HS and fatigue scores were not different between the bottle feeding groups.

Table 2 Health status and fatigue between sufficient and insufficient vitamin D levels in breastfeeding women [a]

	Breastfeeding	
	Sufficient vitamin D (n=25)	**Insufficient vitamin D (n=33)**
SF-36		
Physical functioning	77.3 (67.9 – 86.8)	77.4 (71.3 – 83.5)
Social functioning	85.3 (74.2 – 96.5)	74.9 (67.8 – 82.0)
Role physical	58.7 (34.6 – 82.8)	51.1 (35.3 – 66.8)
Role emotional	93.9 (76.9 – 110.8)	80.4 (69.4 – 91.5)
Mental health	89.0 (83.2 – 94.9)	83.9 (80.1 – 87.6)
Vitality	60.5 (52.7 – 68.4)	65.7 (60.7 – 70.8)
Bodily pain	86.9 (77.0 – 96.8)	77.9 (71.5 – 84.2)
General health	82.0 (76.0 – 88.0)	78.9 (75.0 – 82.7)
Health change	49.1 (39.0 – 59.2)	46.5 (40.0 – 53.0)
Physical component summary	75.2 (65.3 – 85.1)	71.5 (65.1 – 77.9)
Mental component summary	82.1 (73.7 – 90.5)	76.6 (71.1 – 82.1)
Total	75.2 (67.3 – 83.1)	71.0 (65.9 – 76.1)
CIS		
Subjective fatigue	27.1 (21.4 – 32.9)	28.7 (25.0 – 32.4)
Reduced motivation	9.6 (7.3 – 12.0)	10.4 (8.9 – 11.9)
Reduced activity	10.8 (8.4 – 13.2)	10.0 (8.5 – 11.5)
Reduced concentration	16.5 (12.5 – 20.5)	15.0 (12.5 – 17.6)
Total	64.6 (53.4 – 75.7)	64.0 (56.9 – 71.1)

Abbreviations: SF-36, 36-item Short Form health survey, and CIS, Checklist individual strength.
[a] Values are given as mean (95% CI), corrected for baseline differences (age, season).
Analyses of covariance (ANCOVA): There were no significant differences between the sufficient vitamin D and insufficient vitamin D group on the variables.

Table 3 Health status and fatigue between sufficient and insufficient vitamin D levels in bottle feeding women [a]

	Bottle feeding	
	Sufficient vitamin D (n=20)	**Insufficient vitamin D (n=35)**
SF-36		
Physical functioning	88.0 (74.0–101.9)	85.3 (74.6–96.0)
Social functioning	80.6 (67.0–94.2)	93.7 (83.2–104.2)
Role physical	74.5 (48.0–101.1)	84.8 (64.4–105.3)
Role emotional	88.6 (70.8–106.4)	97.0 (83.3–110.7)
Mental health	84.2 (73.8–94.5)	86.5 (78.5–94.5)
Vitality	72.8 (60.8–84.7)	68.4 (59.2–77.6)
Bodily pain	88.4 (73.2–103.7)	85.9 (74.1–97.6)
General health [b]	84.8 (70.9–98.7)	70.0 (59.3–80.7)
Health change	51.2 (37.3–65.1)	48.7 (38.0–59.4)
Physical component summary	83.9 (69.5–98.4)	81.5 (70.4–92.6)
Mental component summary	81.5 (70.4–92.7)	86.4 (77.8–95.0)
Total	79.2 (69.0–89.5)	80.0 (72.1–87.9)
CIS		
Subjective fatigue	23.9 (14.9–32.8)	25.1 (18.3–32.0)
Reduced motivation	7.8 (4.6–11.0)	8.0 (5.6–10.5)
Reduced activity	5.8 (2.5–9.1)	6.9 (4.4–9.4)
Reduced concentration	14.5 (8.2–20.8)	12.9 (8.1–17.7)
Total	52.3 (34.0–70.5)	53.4 (39.4–67.3)

Abbreviations: SF-36, 36-item Short Form health survey, and CIS, Checklist individual strength.
[a] Values are given as mean (95% CI), corrected for baseline differences (highest education, season, vitamin use).
[b] Analyses of Covariance (ANCOVA) p = 0.035.
Note: There were no significant differences between the sufficient vitamin D and insufficient vitamin D group on the other variables.

Linear regression analysis showed no association of infant feeding method with vitamin D concentration (ß = 0.00; p = 1.00). Regarding season, summer (ß = 0.72; p < 0.0001) and fall (ß = 0.24; p = 0.011) were significantly associated with vitamin D concentration. Vitamin supplementation (ß = 0.27; p < 0.0001) and Caucasian ethnicity (ß = 0.18; p = 0.015) were also significantly associated with vitamin D concentration. The explained variance (R^2) was 47%.

Discussion

The current study shows that more than half of the women had insufficient vitamin D levels at 5 weeks postpartum, with no difference between the breastfeeding and bottle feeding women. Vitamin D concentration in postpartum women was

associated with season of inclusion, vitamin supplementation, and ethnicity. Scores on the SF-36 general health scale were significant worse in the bottle feeding women with insufficient vitamin D levels.

To our knowledge, this is the first study that reports the prevalence of postpartum vitamin D insufficiency in both lactating women as in women who bottle-feed their infant. It is also the first study reporting complete HS (physical, mental, and social functioning) and fatigue comparing vitamin D insufficient and sufficient postpartum women.

Several limitations need to be addressed. Women were only included in the present study if an indication for Hb determination existed. Hb level was not different between the study groups and seems therefore not associated with vitamin D status. Also, we performed linear regression analyses and found no association of Hb level, amount of blood loss, mode of delivery, manual removal of the placenta, and clinical symptoms of anemia with vitamin D concentration (data not shown).
No clear definition exists for vitamin D insufficiency, but most agree that a 25-OH vitamin D serum level of at least 50 nmol/L is needed to avoid bone problems [1, 14]. Therefore, we also used this cut-off value. Due to the small sample size we did not examine vitamin D deficiency, insufficiency, and sufficiency with regard to infant feeding method. Vitamin D deficiency (25-OH-vitamin D < 25 nmol/L) was present in 6 women in the breastfeeding group and 9 in the bottle feeding group (10.3% versus 16.4%, $p = 0.35$). There were no differences in HS and fatigue when comparing vitamin D deficient, insufficient and sufficient postpartum women (data not shown).
Dietary intake of vitamin D containing products was not addressed in this study. However, the major source of vitamin D is sunlight, and a recent review showed that vitamin D intake is consistently below nutrient recommendation levels in pregnant women in developed countries [1, 22].

Vitamin D insufficiency (< 50 nmol/L) is a worldwide problem with a prevalence ranging from 23% of Danish and 99.7% of Indian breastfeeding women [6, 7]. The present study found insufficient vitamin D levels in 57% of the breastfeeding women. The difference in prevalence may be caused by differences in diet, vitamin supplementation use, sun exposure, and skin color [23-25].

The statistical significant difference on the SF-36 general health scale between the bottle feeding groups is more likely to reflect multiple testing or chance, than a

difference with clinical meaning since general health was not different between the breastfeeding groups.

In contrast to a previous study in premenopausal women with inadequate vitamin D levels, we observed no association between inadequate vitamin D levels and HS in postpartum women [5]. Also, fatigue scores were not different between the vitamin D sufficient and insufficient groups, which is in contrast with previous studies that associated fatigue with inadequate vitamin D levels in general practice [2-4]. In present study, a higher vitamin D concentration was associated with summer and fall, vitamin supplementation, and ethnicity (being Caucasian), which corresponds with the literature [23-25].

International guidelines recommend vitamin D supplementation for pregnant and lactating women [14, 15, 25]. If an indication for vitamin D supplementation includes high frequency of inadequate vitamin D levels to maintain bone health, all postpartum women should be supplemented instead of only the lactating women.

The present study was conducted in the Netherlands, most women were Caucasian, and indication for inclusion were Hb determination; therefore these results cannot be extrapolated to all postpartum women and to not Western countries. Future research should focus on HS, fatigue, and co-morbidity after vitamin D supplementation during the postpartum period.

Conclusion

More than half of the postpartum had insufficient vitamin D levels, which was as frequent in lactating women as in women who bottle-fed their infant. A higher vitamin D concentration was associated with season of inclusion (summer or fall), vitamin supplementation, and ethnicity (being Caucasian), but not with HS and fatigue. In order to ensure good bone health, the international recommendation for supplementation of 10 – 15 micrograms vitamin D per day should also include postpartum women who bottle feed their infants.

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Chapter 5

Vitamin B12 in postpartum women: a prospective cohort study

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Submitted

Abstract

Objective: To assess the prevalence of vitamin B12 deficiency in the first five weeks postpartum, and to examine the fraction of active vitamin B12.

Design: A prospective cohort study.

Setting: Large teaching hospital in Tilburg, the Netherlands.

Population: 171 postpartum women.

Methods: Total vitamin B12 and holotranscobalamin (holoTC) were measured within 48 hours (T0) and at 5 weeks (T5) postpartum. Vitamin B12 deficiency was defined as total vitamin B12 < 180 pmol/L or holoTC < 32 pmol/L. The fraction of active vitamin B12 was defined as holoTC/total vitamin B12.

Main outcome measures: Vitamin B12 deficiency at T0 and T5 based on total vitamin B12 and holoTC, and the fraction of active vitamin B12 in vitamin B12 deficient women.

Results: Without intervention, vitamin B12 deficiency based on both serum vitamin B12 and holoTC changed from 75% and 60% at T0, to respectively 10% and 6% at T5. Total vitamin B12 deficient women had a significant higher fraction of active vitamin B12 compared with not deficient women at both T0 ($p < 0.0001$, mean 0.25 ± SD 0.12 and mean 0.19 ± SD 0.07) and T5 ($p < 0.0001$, mean 0.28 ± SD 0.08 and mean 0.21 ± SD 0.06). The vitamin B12 deficiency group had a higher fraction of active vitamin B12 compared with the not vitamin B12 deficiency group ($p = 0.002$).

Conclusions: The results suggest physiological changes of vitamin B12 postpartum with a shift towards the metabolic active vitamin B12 (holoTC) in women with insufficient available total vitamin B12. Postpartum women without risk factors or manifestations of a true vitamin B12 deficiency do not need vitamin B12 supplementation.

Introduction

Serum vitamin B12 (cobalamin) concentrations show a significant decrease in each trimester during pregnancy to marginal or non-pregnant deficient values in healthy pregnant women [1-4]. Postpartum, vitamin B12 concentrations spontaneously recover to preconceptional values [1, 5]. However, serum vitamin B12 measurement has a low positive predictive value, meaning that a low serum vitamin B12 level not always indicates an actual vitamin B12 deficiency at tissue level [6]. Therefore, supplementation of vitamin B12 in the absence of manifestations of deficiency is a matter of debate in the current literature [6, 7].

Several studies conclude that the observed change of serum vitamin B12 during pregnancy and postpartum is physiologic [1, 2]. Despite depressed vitamin B12 concentrations, homocysteine and methylmalonic acid levels were not elevated as would be expected in vitamin B12 deficiency [1-3, 5, 8]. Also, a concomitant increase in erythrocyte cobalamin was observed [2]. Explanations for the cobalamin reduction are hemodilution, transportation to the fetus, and redistribution of cobalamin. However, serum vitamin B12 concentrations during pregnancy decline more than can be accounted for by hemodilution [8]. Also, the total requirement of the fetus during pregnancy is estimated to be 50 µg, while maternal stores in women with mixed diet are estimated at > 1000 µg [9]. Therefore, in well-nourished women, body stores of vitamin B12 are adequate to meet fetal needs during gestation [10]. The combination of a decrease in total serum vitamin B12, the increase in erythrocyte cobalamin, and a decrease in saturation of cobalamin binding serum proteins suggests a redistribution of cobalamin [2].

Only 20% of serum vitamin B12 is bound to transcobalamin (holoTC), which is the active part of vitamin B12 available for tissue uptake [11]. The remaining 80% is bound to haptocorrin (holohaptocorrin, holoHC) and has no known biological function [12]. Several studies showed that HoloTC remains constant during pregnancy and postpartum [1, 5], while holoHC decreases during pregnancy [2]. Our hypothesis is that a shift occurs towards holoTC in women with insufficient available total vitamin B12. Therefore, the fraction of active vitamin B12 (holoTC/total vitamin B12) will be higher in women with vitamin B12 deficiency. Our objectives were to examine the prevalence of vitamin B12 deficiency based on total vitamin B12 and holoTC directly and at five weeks postpartum, and to compare the fraction of active vitamin B12 between vitamin

B12 deficient and not deficient women during the first weeks postpartum. We also examined the effect of postpartum multivitamin use on vitamin B12 deficiency and fraction of active vitamin B12 at 5 weeks postpartum.

Materials and methods

Study design and population

The current prospective study was performed between April 2008 and August 2010 at a large teaching hospital in Tilburg, in the southern part of the Netherlands. The study was approved by the local ethics committee (file number NL21797.028.08). All women received oral and written information about the study and provided oral and written informed consent. Women were eligible for inclusion if they were ≥ 18 years old, thoroughly understood the Dutch language, and had indications for blood sampling within 48 hours after delivery, including estimated blood loss > 500 ml, delivery by cesarean section, manual removal of the placenta, and clinical symptoms of anemia. Women were excluded if: their hemoglobin was < 6.4 g/dL (because the hospital protocol indicates the need for packed red cell transfusion); they were addicted to alcohol or drugs; they had hematological disease; they had chronic inflammatory disease; or they were being treated with methotrexate.

Procedure

Maternal venous blood was collected in the hospital within 48 hours after delivery (T0) and at five weeks postpartum (T5) in the outpatient clinic. The women were not informed of their vitamin B12 levels. None of the women received vitamin B12 supplementation. If they used multivitamins, they were allowed to continue them.

Total vitamin B12 was measured on an Advia Centaur immunoassay system (Siemens Healthcare Diagnostics, Breda, The Netherlands). HoloTC was measured in each serum sample using an AxSYM immunoassay analyzer (Abbott Diagnostics, Hoofddorp, The Netherlands). These parameters were measured in control and analyzed in the normal diagnostic practice of the laboratory. In our hands, the respective between-run coefficients of variation for vitamin B12 and holoTC were 3.1 % (at a vitamin B12 level of 180 pmol/L) and 4.3 % (at a holoTC level of 30 pmol/L).

Outcomes

Vitamin B 12 deficiency was defined as total vitamin B12 < 180 pmol/L or holoTC < 32 pmol/L [13]. The fraction of active vitamin B12 was defined as holoTC/total vitamin B12 [14].

Statistical analyses

Statistical analyses were performed using SPSS 20.0. Continuous variables at baseline were compared by independent sample T-tests and nominal variables by Chi-square tests. The McNemar test was used to determine the distribution of vitamin B12 and holoTC deficiency from T0 to T5. The independent sample T-test was used to determine the difference in fraction of active vitamin B12 between the vitamin B12 deficient and not deficient women at T0 and T5. Analysis of variance for repeated measures was used to compare the mean fraction of active vitamin B12 between vitamin B12 deficient and not deficient women. The effect of postpartum multivitamin use on vitamin B12 deficiency and fraction of active vitamin B12 at T5 was assessed using Chi-square and independent T-test. All results were reported as the mean ± standard deviation (SD), or percentage (%), as appropriate.

Results

A total of 171 women were included in the study. The demographic and clinical characteristics of the participants at baseline are shown in Table 1.

Table 1 Patient demographic and clinical characteristics at baseline (T0)

	Vitamin B12 < 180 pmol/L	**Vitamin B12 ≥ 180 pmol/L**
	(n=129)	**(n=42)**
Age at entry (years)	30.5 ± 4.6	31.3 ± 3.8
BMI before pregnancy (kg/m²)	25.7 ± 5.8	24.8 ± 4.9
Twin pregnancies	2 (1.6)	1 (2.4)
Ethnicity		
Caucasian	117 (90.7)	39 (92.9)
Turkish	4 (3.1)	0 (0.0)
African	4 (3.1)	1 (2.4)
Asian	2 (1.6)	1 (2.4)
South American	2 (1.6)	1 (2.4)
Smoking	13 (10.1)	3 (7.1)
Diet		
Omnivore	78 (60.5)	27 (64.3)
Vegetarian	4 (3.1)	0 (0.0)
Unknown	47 (36.4)	15 (35.7)
Multivitamin use [1]	43/101 (42.6)	21/36 (58.3)
Parity at baseline	1.5 ± 0.7	1.3 ± 0.6
Gestational age at delivery (weeks)	39.9 ± 1.5	39.5 ± 1.5
Delivery method		
Vaginal	53 (41.4)	13 (31.0)
Cesarean section	76 (58.6)	29 (69.0)
Infant birth weight (gram)	3510.5 ± 553.5	3435.1 ± 493.2
Infant feeding:		
Breastfeeding	78 (60.5)	26 (61.9)
Bottle (formula) feeding	51 (39.5)	16 (38.1)
Holotranscobalamin [a]		
< 32 pmol/L	86 (66.7)	16 (38.1)
≥ 32 pmol/L	43 (33.3)	26 (61.9)

Numbers are mean ± SD or number (percentage)
[1] Unknown multivitamin use, n=34
[a] Chi square: p = 0.001
Note: There were no significant differences between the vitamin B12 deficient and not deficient group on the other variables.

Vitamin B12 deficiency

HoloTC deficiency was significant more prevalent in women with total vitamin B12 deficiency, and normal holoTC values were more prevalent in women with normal total vitamin B12 values (p = 0.001, Table 1).

Table 2 shows the significant differences in distribution of total vitamin B12 deficiency and holoTC deficiency from T0 to T5 (p < 0.0001). Vitamin B12 deficiency within 48 hours postpartum was prevalent in 75% of the women based on total vitamin B12 values, and in 60% of the women based on holoTC. At T5, vitamin B12 deficiency was prevalent in 9.9% based on total vitamin B12 values, and 5.8% based on holoTC. Of the 129 vitamin B12 deficient women at T0, only 17 (9.9%) remained deficient at T5. Ten (5.8%) of the 102 holoTC deficient women at T0 remained deficient at T5. All women with normal vitamin B12 (n = 42, 24.6%) and holoTC values (n = 69, 40.4%) on T0, continued to have normal values on T5.

Table 2 Distribution of vitamin B12 and holotranscobalamin (holoTC) deficiency within 48 hours postpartum (T0) and at 5 weeks postpartum (T5)

		Vitamin B12 T5		
		< 180 pmol/L	≥ 180 pmol/L	Total
Vitamin B12 T0	< 180 pmol/L	17 (9.9)	112 (65.5)	129 (75.4)
	≥ 180 pmol/L	0 (0.0)	42 (24.6)	42 (24.6)
	Total	17 (9.9)	154 (90.1)	171 (100.0)

Numbers (percentage)
McNemar test: p < 0.0001

		HoloTC T5		
		< 32 pmol/L	≥ 32 pmol/L	Total
HoloTC T0	< 32 pmol/L	10 (5.8)	92 (53.8)	102 (59.6)
	≥ 32 pmol/L	0 (0.0)	69 (40.4)	69 (40.4)
	Total	10 (5.8)	161 (94.2)	171 (100.0)

Numbers (percentage)
McNemar test: p < 0.0001

Fraction of active vitamin B12

Total vitamin B12 deficient women had a significant higher fraction of active vitamin B12 compared with not deficient women at both T0 (p < 0.0001, mean 0.25 ± SD 0.12 and mean 0.19 ± SD 0.07) and T5 (p < 0.0001, mean 0.28 ± SD 0.08 and mean 0.21 ± SD 0.06). A high fraction of active vitamin B 12 (> 0.40) was only present in women with total vitamin B12 deficiency at T0 (n = 13, Figure 1a). Of these, 85% (n = 11) had a normal holoTC level. At T5, no high vitamin B12 fraction was found (Figure 1b).

Figure 1a Fraction of active vitamin B12 and holotranscobalamin (holoTC) between vitamin B12 deficient and not deficient women within 48 hours postpartum (T0)

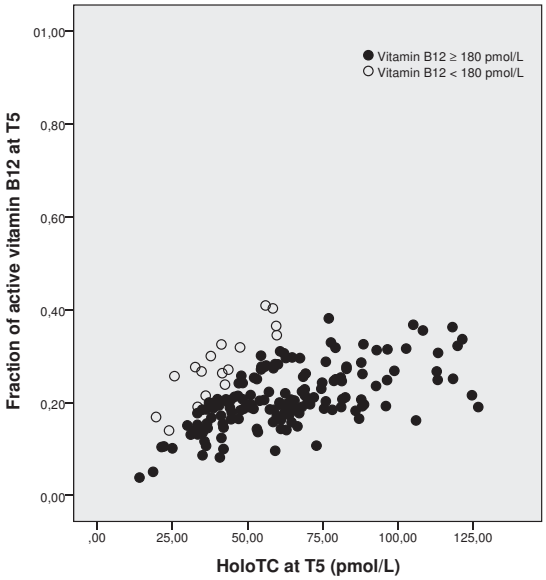
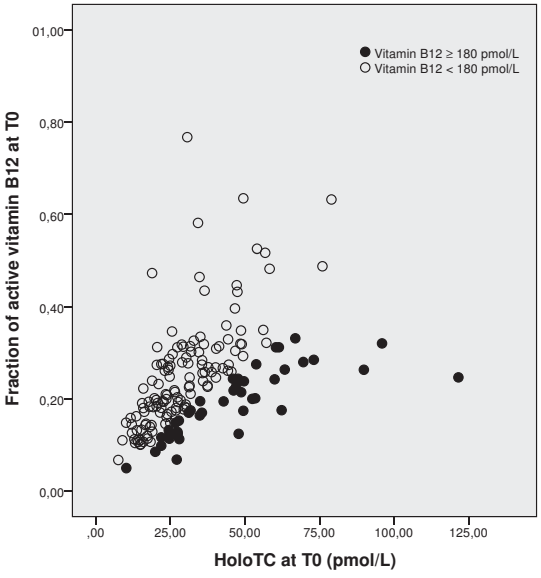


Figure 1b Fraction of active vitamin B12 and holotranscobalamin (holoTC) between vitamin B12 deficient and not deficient women at 5 weeks postpartum (T5)



Repeated measures ANOVA showed that there was no interaction effect of fraction of active vitamin B12 and vitamin B12 deficiency (based on total vitamin B12, p = 0.054). Also, there was no effect of time with regard to active vitamin B12 fraction (p = 0.11). However, a significant group effect for the fraction of active vitamin B12 was observed (p = 0.002). The vitamin B12 deficiency group had a higher fraction of active vitamin B12 compared with the not vitamin B12 deficiency group.

Multivitamin use

At T5, multivitamin use of the included women was known in 137 of the 171 women; 52 women (38%) used multivitamins, and 85 women did not use multivitamins (62%). There were no significant differences in vitamin B12 deficiency between the groups who did and did not use multivitamins at T5, based on both vitamin B12 (p = 0.45) and holoTC (p = 0.13). Also, no significant difference in fraction of active vitamin B12 was found between the groups who did and did not use multivitamins at T5 (p = 0.58).

Discussion

Main findings

Without intervention, vitamin B12 deficiency based on both serum vitamin B12 and holoTC changed from 75% and 60% at T0, to respectively 10% and 6% at T5. All women with normal serum vitamin B12 and holoTC values within 48 hours postpartum continued to have normal values at 5 weeks postpartum. The fraction of active vitamin B12 was significant higher in vitamin B12 deficient women at both time points and across time. A high fraction of active vitamin B 12 was only present in women with total vitamin B12 deficiency at T0. At T5, no high vitamin B12 fraction was found.

Strengths and weaknesses

The present study is limited by selection bias. All included women had indication for blood sampling based on potential anemia. However, earlier studies found no association of hemoglobin level and vitamin B12 status during pregnancy and postpartum [1, 2]. Homocysteine and methylmalonic acid levels were not measured to define vitamin B12 deficiency in the present study. However, earlier studies found no significant correlation between homocysteine or methylmalonic acid and vitamin B12 deficiency, both during pregnancy and postpartum [1, 5]. Another limitation of

the study is that in 36% of the included women the diet is unknown. Women who are vegetarian or vegan are at increased risk of vitamin B12 deficiency [6]. Yet, we believe that this has not affected our results. The four included vegetarian women in the present study were vitamin B12 deficient within 48 hours postpartum. Without the use of multivitamins, they all reached normal holoTC values at five weeks postpartum (data not shown).

Interpretation

The results of the present study show that the fraction of active vitamin B12 is higher in postpartum women with insufficient available serum vitamin B12, which suggests a shift towards the metabolic active vitamin B12 (holoTC). The spontaneous disappearance of vitamin B12 deficiency from directly postpartum to 5 weeks postpartum probably reflects physiological changes during the postpartum period rather than a true vitamin B12 deficiency. Earlier studies confirm these physiological changes. Despite depressed vitamin B12 concentrations, no elevation of homocysteine and methylmalonic acid levels were found, and an increase in erythrocyte cobalamin was found [1, 2].

To our knowledge, this is the first study reporting the course of serum vitamin B12, holoTC and fraction of active vitamin B12 in the first weeks postpartum. Based on serum vitamin B12, the prevalence of vitamin B12 deficiency in the present study was higher within 48 hours postpartum compared with the third trimester of pregnancy in the current literature (75% versus 35 to 43%) [1, 2]. Therefore, it seems that total vitamin B12 levels even decrease from the third trimester of pregnancy to immediately postpartum. The prevalence of vitamin B12 deficiency at 5 weeks postpartum in the present study is considerably higher compared with the prevalence as reported in a previous study on vitamin B12 deficiency at 8 weeks postpartum (10% versus 3%) [1]. This could be explained by the difference in time of measurement postpartum. It is expected that the serum vitamin B12 can spontaneously improve from 5 weeks to 8 weeks postpartum. The present study showed a significant increase of mean holoTC from T0 to T5 ($p < 0.0001$, mean 33.3 SD ±17.5 to 60.6 SD ± 24.0), which does not correspond to earlier studies which found that holoTC remains constant during pregnancy and postpartum [1, 5]. However, these studies measured holoTC at the third trimester of pregnancy and at 8 weeks postpartum, and not immediately postpartum.

Conclusion

The results of the present study suggest physiological changes of vitamin B12 postpartum with a shift towards the metabolic active vitamin B12 (holoTC) in women with insufficient available total vitamin B12.

Because this study included women of different ages and parity, the results are applicable in daily medical practice. Supplementation of vitamin B12 in postpartum women can result in overtreatment. Therefore, postpartum women without risk factors or manifestations of a true vitamin B12 deficiency do not need vitamin B12 supplementation. The present study was conducted in the Netherlands, and most women were Caucasian with western dietary habits Therefore, these results cannot be extrapolated to countries with a high prevalence of vegetarian diets.
Future research should focus on postpartum vitamin B12 deficiency in women with different diet and ethnic backgrounds.

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Chapter 6

An added value for the hemoglobin content in reticulocytes (CHr) and the mean corpuscular volume (MCV) in the diagnosis of iron deficiency in postpartum anemic women

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Abstract

Introduction: To evaluate the use of reticulocyte hemoglobin content (CHr) and mean corpuscular volume (MCV) to identify truly iron deficient women with postpartum anemia (PPA), in order to reduce unnecessary iron supplementation.

Methods: Three hundred women with more than 500 mL of blood loss or clinical signs of anemia were divided in a control (hemoglobin [Hb] ≥ 10.5 g/dL, n = 150) and PPA group (Hb < 10.5 g/dL; n = 150). PPA women were given ferrous fumarate for a period of 4 weeks. Efficacy of the treatment was evaluated by comparing Hb, CHr, and MCV at baseline (T0) and after 4 weeks (T4). Using standard iron deficiency cut off values for MCV (80 fL) and CHr (28 pg) at T0, we divided the PPA group of both parameters into two subgroups, one suggestive for iron deficiency and one suggestive for non-iron deficiency.

Results: Irrespective of the parameter or the subdivision, delta Hb concentrations (T4–T0) showed a similar increase in all PPA subgroups investigated. Both parameters in the PPA subgroups below their respective cut off value showed a significant improvement towards normalization, while the MCV and CHr in the PPA subgroups above their respective cut off value did not show any significant increase.

Conclusion: Our data suggest that the etiology of the anemia in postpartum anemic women is not always iron deficiency. Using a combination of Hb, MCV and CHr, we increased the stringency to identify truly iron-deficient postpartum anemic women, thereby reducing unnecessary iron supplementation in those women with sufficient iron stores.

Introduction

Postpartum anemia (PPA) occurs frequently and is an important risk factor for maternal morbidity [1–3]. The prevalence of PPA varies considerably in the different studies, ranging from 22% to 27% [4, 5], with the highest prevalence in women with a low socioeconomic status [5]. Anemia in non-pregnant women is defined by the World Health Organization as a hemoglobin (Hb) concentration of < 12 g/dL (7.5 mM x 1.611) [6]. Although there is no clear cut off value for PPA in literature, the Dutch Society of Obstetrics and Gynecology-guideline for anemia uses a cut off value of 10.5 g/dL [7]. The difference in cut off value between non-pregnant and pregnant women is explained by the attempt to correct for the physiological hemodilution as present in pregnancy [8] and, more importantly, because of blood loss during labor. Because of this, added to the increased demand for iron during pregnancy, it is assumed that the most probable cause of anemia in the postpartum period is because of iron deficiency. While in our hospital, severe PPA (Hb < 6.5 g/dL) is treated with transfusion of packed red blood cells, treatment of mild PPA (6.5 ≤ Hb < 10.5 g/dL) consists of oral iron supplementation.

Ferrous fumarate is the most commonly used iron compound in Dutch obstetric practice. While severe side effects of iron supplementation (i.e., iron overload) are restricted to rare entities such as thalassemia or hemochromatosis (either congenital or acquired), most side effects are mild but nevertheless inconvenient, resulting in gastro-intestinal complaints such as nausea, diarrhea, or constipation [9].

Most anemia protocols make use of multiple laboratory parameters to unravel the etiology of the anemia at hand. However, in dealing with mild PPA, it is assumed that the most probable cause of the anemia is iron deficiency and consequently is treated as such. This assumption disregards the fact that some PPA women with sufficient iron stores have no beneficial effect of supplementation.

The reticulocyte hemoglobin content (CHr) is a relatively new measure for iron deficiency. Using the Prussian blue staining of a bone marrow aspirate to define iron deficiency, CHr outperformed the traditional markers like ferritin, transferrin saturation, and mean corpuscular volume (MCV) for the diagnosis of iron deficiency [10]. CHr is a parameter that can be measured on an Advia platform (Siemens Healthcare Diagnostics, Breda, Netherlands). However, comparable measurements of the reticulocyte hemoglobin content are available on other platforms [11, 12].

In this study, we investigate the use of the CHr together with the MCV to establish whether or not iron deficiency is the true cause of the PPA, thereby preventing unnecessary supplementation and as a consequence averting potential side effects of iron supplementation in non-iron deficient women. Ferritin is also a well-established parameter for diagnosing iron deficiency anemia. However, in concurrence with the literature, we decided against using ferritin as a marker for iron deficiency in PPA women because of its prominent role in the acute phase response during parturition [13, 14].

Methods

Population

The source population consisted of women who delivered in the TweeSteden hospital in the period between January 2007 and December 2008. Table 1 shows an overview of all inclusion and exclusion criteria. Women aged 18 years or older, with more than 500 mL of blood loss during labor or with clinical signs of anemia (e.g., fatigue, loss of stamina, headache, faintness, pale skin, pale mucous membranes, hypotension, or tachycardia) were asked to join the study. After obtaining informed consent, all included women undergone blood testing (see below). Based on their Hb concentration, subjects were divided in a non-anemic control group (Hb ≥ 10.5 g/dL; n = 150) and a PPA index group (6.5 ≤ Hb < 10.5 g/dL; n = 150). Women with extreme PPA (Hb < 6.5 g/dL) were excluded because of packed red blood cells transfusion. The non-anemic control group did not receive any prescribed medication. The PPA index group received ferrous fumarate (200 mg x 3 tablets a day) for a period of 4 weeks.

Table 1 Overview of all inclusion and exclusion criteria

Inclusion	Exclusion
Women aged > 18 years	Vitamin B12 deficiency (< 160 pm)
Thorough grasp of Dutch language	Packed cell infusion in the previous 3 months
Informed consent acceptance	Alcohol/drug addiction
Delivery in a clinical obstetric setting	Chronic infection
0 – 48 h after delivery	Gastro-intestinal disease
> 500 mL blood loss or clinical signs of anemia	Thalassemia/hemoglobinopathy
	Aplastic, megaloblastic, or hematolytic anemia
	Malignant disease
	Kidney failure
	Liver failure
	Bone marrow disease
	Methothrexate use (interaction with folic acid)
	Contra-indications folic acid use
	Contra-indications ferrous fumarate use

Criteria were checked during a thorough interview

Laboratory parameters

Both the non-anemic control and the PPA index group were subjected to blood testing at the time of inclusion (T = 0 weeks, T0, being 0–48 hours after delivery) and during follow-up (T = 4 weeks, T4). The following parameters were tested: Hb, MCV, and CHr. These red blood cell parameters were measured in K2EDTA anti-coagulated blood on an ADVIA2120i or ADVIA120 Hematology platform (Siemens Healthcare Diagnostics Breda, The Netherlands). All parameters were measured in control and analyzed in the normal diagnostic practice of our laboratory. For the MCV and CHr, the respective coefficients of variation of control material were 1.55 (target value 85 fL) and 1.00% (target value 23 pg).

Cut off values for MCV and CHr for iron deficiency

The MCV is a widely accepted erythrocyte index and is one of the first parameters to be analyzed in most anemia protocols. With the prerequisite that the Hb concentration is below the reference interval, an MCV of below 80 fL is indicative for iron deficiency [15]. Note that severe microcytosis (i.e., < 72 fL) is more suggestive for hemoglobinopathies [16].

The CHr is the product of the cellular volume and the Hb concentration of reticulocytes [17]. Compared to the slow turnover of erythrocytes (~ 120 days), reticulocytes have an average life span of 4 days, making the CHr a much more dynamic parameter compared to the standard erythrocytes indices. For adults, a CHr cut off value of < 28 pg is used for the diagnosis of iron deficiency [10].

Group analysis

Based on literature and clinical guidelines regarding iron deficiency anemia [6,10,18], cut off values for MCV (< 80 fL) and CHr (< 28 pg, i.e., 1.74 fmol) were used to create PPA subgroups. For both parameters, this created three groups: a non-anemic control group and two ferrous fumarate-supplemented PPA groups, one with patients below the above mentioned cut off values and the other with patients above the cut off values. For all patients, parameter changes between T0 and T4 were calculated and expressed as delta-values (T4–T0, dHb, dMCV, dCHr). Normality of distribution of the individual parameters was verified using a one sample Kolmogorov–Smirnov test. Statistical analysis was performed using a paired (T0 vs. T4) T-test. Pearson's product-moment correlation coefficient was calculated to assess the association between MCV and CHr (SPSS PASW 17.0.2; IBM, New York, NY, USA).

Results

Non-anemic vs. anemic women

Table 2 shows an overview of the changes in Hb, MCV, and CHr between To and T4 in the non-anemic control and PPA group. Both the non-anemic and supplemented anemic group showed a significant increase in Hb at T4 when compared to To ($p < 0.001$). This increase was more prominent in the anemic group compared to the non-anemic control group, 3.4 vs. 1.6 g/dL, respectively. The increase in MCV in the PPA group at T4 is statistically significant compared to To ($p < 0.001$). However, the delta MCV of +1.2 fL falls within the 1.55% coefficient of variation (CV) of the MCV assay. In the PPA group, CHr at T4 did not (significantly) change compared to To (dCHr 0.0 pg).

Table 2 Changes in iron deficiency laboratory parameters between T = 0 weeks (To) and T = 4 weeks (T4) in the non-anemic control and PPA index group

Parameter	Group	n	To	T4	Delta (T4-To)
Hb (g/dL)	Non-anemic	101	11.4 (0.8)	13.0 (0.8)*	+1.6
	PPA	115	9.0 (1.0)	12.4 (1.0)*	+3.4
MCV (fL)	Non-anemic	101	86.2 (4.0)	85.5 (4.0)	-0.7
	PPA	115	83.2 (6.0)	84.4 (6.0)*	+1.2
CHr (pg)	Non-anemic	90	31.6 (2.4)	30.8 (2.1)*	-0.8
	PPA	105	29.8 (2.9)	29.8 (2.6)	0.0

Abbreviations: PPA = postpartum anemia, Hb = hemoglobin, MCV = mean corpuscular volume, CHr = reticulocyte hemoglobin content

Data in columns To and T4 are shown as mean (SD)

*$p < 0.001$ vs. To.

Note: although at To 150 women were included, some were lost to the study during follow-up at T4. Because of the preferred paired statistical analysis between To and T4, this lowered the group size (n) of the parameters.

PPA MCV subgroups

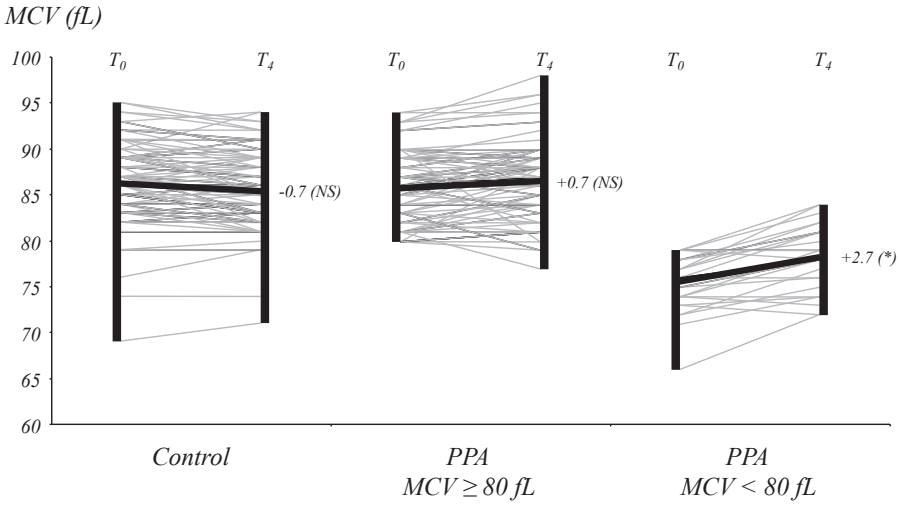
By dividing the PPA group at To in a microcytic (MCV < 80 fL) and normocytic (MCV ≥ 80 fL) anemia subgroup, we created two MCV subgroups. Irrespective of the subdivision, both subgroups showed an increase in Hb at T4 of +2.9 and +3.4 g/dL for microcytic and normocytic PPA women, respectively ($p < 0.001$, Table 3). However, in microcytic PPA women, the increase in MCV (dMVC +2.7 fL) was significant ($p < 0.001$) and well outside the 1.55% CV of the assay. In contrast, the MCV of normocytic PPA women showed an insignificant increase of +0.7 fL (Table 3, Figure 1a).

Table 3 Changes in Hb and MCV between T = 0 weeks (T0) and T = 4 weeks (T4) in the non anemic control, low MCV (< 80 fL) PPA, and normal MCV (≥ 80 fL) PPA group

Parameter	Group	n	T0	T4	Delta (T4-T0)
Hb (g/dL)	Non-anemic	101	11.4 (0.8)	13.0 (0.8)*	+1.6
	PPA (MCV < 80 fL)	30	8.9 (1.0)	11.8 (1.1)*	+2.9
	PPA (MCV ≥ 80 fL)	85	9.2 (1.0)	12.6 (0.8)*	+3.4
MCV (fL)	Non-anemic	101	86.2 (4.0)	85.5 (4.0)	-0.7
	PPA (MCV < 80 fL)	30	75.5 (3.0)	78.2 (3.0)*	+2.7
	PPA (MCV ≥ 80 fL)	85	85.8 (4.0)	86.5 (4.0)	+0.7

Abbreviations: PPA = postpartum anemia, Hb = hemoglobin, MCV = mean corpuscular volume
Data in columns T0 and T4 are shown as mean (SD).
*p < 0.001 vs. T0.

Figure 1a MCV from T = 0 weeks (T0) to T = 4 weeks (T4) in the non-anemic control, normal MCV (≥ 80 fL) PPA, and low MCV (< 80 fL) PPA groups



Mean (thick black lines) and individual (thin black lines) delta MCV (dMCV, T4–T0) in non-anemic control, PPA normal MCV (MCV ≥ 80 fL), and PPA low MCV subgroups (MCV < 80 fL)
T0: T = 0 weeks, T4: T = 4 weeks, NS: not significant
*p < 0.001 vs. T0

PPA CHr subgroups

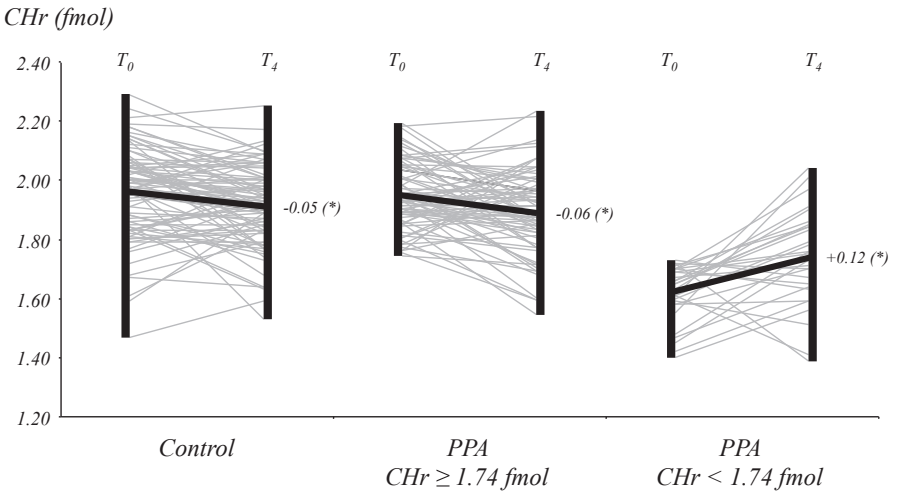
When anemic women were divided based on their CHr [e.g., low CHr (<28 pg) and normal CHr (≥ 28 pg)], no difference was found in the increase in Hb concentration at T4 (Table 4). The mean CHr at T0 in the low CHr subgroup was 26.1 pg and increased by +1.9 pg reaching the CHr cut off value of 28 pg at T4 (p < 0.001). Conversely, the CHr in the normal CHr subgroup (T0, 31.4 pg) decreased by -1.0 pg (p < 0.001, Figure 1b). The decrease in the PPA normal CHr subgroup was similar to the decrease in the non-anemic control group (dCHr -0.8 pg, Table 4).

Table 4 Changes in Hb and CHr between T = 0 weeks (To) and T = 4 weeks (T4) in the non-anemic control, low CHr (< 28 pg) PPA, and normal CHr (≥ 28 pg) PPA group

Parameter	Group	n	To	T4	Delta (T4-To)
Hb (g/dL)	Non-anemic	90	11.4 (0.8)	13.0 (0.8)*	+1.6
	PPA (CHr < 28 pg)	30	8.9 (1.1)	11.9 (1.1)*	+3.0
	PPA (CHr ≥ 28 pg)	75	9.2 (1.0)	12.6 (1.0)*	+3.4
CHr (pg)	Non-anemic	90	31.6 (2.4)	30.8 (2.1)*	-0.8
	PPA (CHr < 28 pg)	30	26.1 (1.4)	28.0 (2.6)*	+1.9
	PPA (CHr ≥ 28 pg)	75	31.4 (1.8)	30.4 (2.3)*	-1.0

Abbreviations: PPA = postpartum anemia, Hb = hemoglobin, CHr = reticulocyte hemoglobin content
Data in columns To and T4 are shown as mean (SD).
*p < 0.001 vs. To.

Figure 1b CHr T = 0 weeks (To) to T = 4 weeks (T4) in the non-anemic control, normal CHr (≥ 28 pg) PPA, and low CHr (< 28 pg) PPA groups

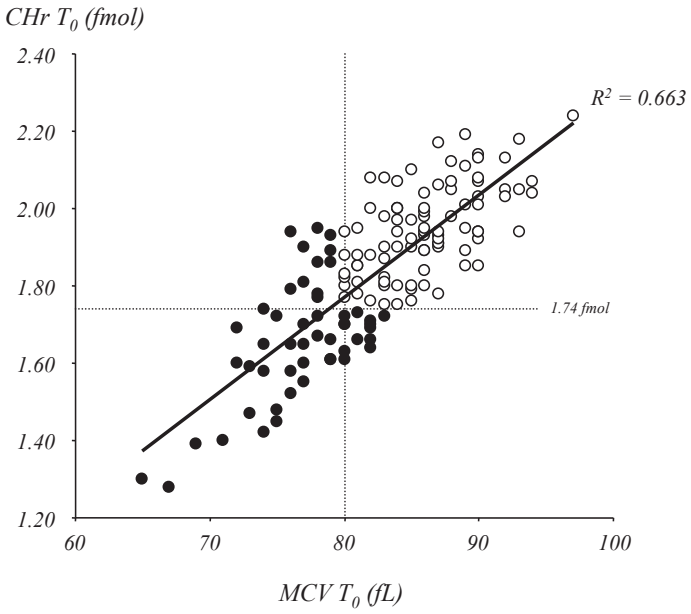


Mean (Thick black lines) and individual (thin black lines) delta CHr (dCHr, T4–To) in non-anemic control, PPA normal CHr (CHr ≥ 28 pg), and PPA low CHr subgroups (CHr < 28 pg)
To: T = 0 weeks, T4: T = 4 weeks
*p < 0.001 vs. To
Note: the non-anemic control and PPA normal CHr showed a significant decrease

MCV vs. CHr correlation

The baseline MCV and CHr values (To) of all PPA women show a good correlation (R^2 = 0.663, p < 0.001, Figure 2). Despite an Hb of < 10.5 g/dL, 64% of the PPA women (89/140) (Figure 2, open dots) had baseline MCV and CHr values above their respective cut off values. 36% of the PPA women (51/140) (Figure 2, closed dots) had a microcytic MCV, a CHr below 28 pg, or both.

Figure 2 Correlation between baseline MCV (x-axis) and CHr values (y-axis) in PPA women



Coefficient of correlation (R^2) is 0.663 ($p < 0.001$).
The vertical and horizontal dotted lines represent the respective cut off values of the MCV (80 fL) and CHr (28 pg).
Open dots: normocytic MCV and CHr above cut off value.
Filled dots: microcytic MCV, CHr below cut off value, or both.

Discussion

In PPA, it is assumed that the etiology of the anemia is attributed to iron deficiency. Consequently, all PPA women with an Hb concentration between 6.5 and 10.5 g/dL are orally supplemented with iron. This potentially results in unnecessary iron supplementation in those women with sufficient iron stores. To evaluate the need for iron supplementation in women with mild PPA, we followed the therapeutic response to iron supplementation using accomplished cut off values for MCV and CHr.

Irrespective of baseline iron deficiency parameters, the Hb concentration in all PPA women improved significantly after 4 weeks (T4). This might be interpreted as a beneficial therapeutic response to iron supplementation for all women with PPA.

Indeed, the PPA MCV and CHr subgroups suggestive for depleted iron stores at T0 showed a significant improvement for both MCV and CHr toward normalization at T4 indicating a beneficial therapeutic response to iron supplementation. However, in the PPA MCV and CHr subgroups arguing against iron deficiency, no improvement in the respective parameters at T4 was seen. The lack of improvement of the MCV and CHr in these subgroups might be explained by the fact that the iron stores at T0 were already adequate and that no additional iron was taken up via the intestines.

The study is limited by the fact that all women with PPA were orally supplemented with iron, lacking a control group with PPA and normal iron stores who were not supplemented with iron. Because intestinal iron uptake is inhibited by hepcidin, which in turn is upregulated by adequate intracellular iron stores [19, 20], we assume that in the PPA group with sufficient iron stores no intestinal iron was taken up. Unfortunately, this remains an assumption because hepcidin concentrations were not measured in this study. Future studies are needed to confirm our findings. One such study would involve randomizing PPA women with adequate baseline iron stores (i.e., normal MCV and CHr ≥ 28 pg) creating PPA groups with and without iron supplementation. Confirming our results, one would expect both groups to show a similar increase in Hb, irrespective of supplementation.

The data of our study suggest that the assumption of iron deficiency as etiology of PPA is not always justified. Indeed, the majority of PPA women in our study (64%) had baseline laboratory parameters (i.e., normocytic MCV and CHr ≥ 28 pg) arguing against iron deficiency as the cause of the anemia and as a result were unnecessarily supplemented with iron.

The MCV and CHr can be readily analyzed in conjunction with an Hb concentration from the same sample. Therefore, next to Hb, we propose to include measurement of MCV and CHr, using standard cut off values, for identifying truly iron-deficient PPA women who will have a beneficial therapeutic response to iron supplementation, thereby reducing the needless supplementation of iron in those PPA women with sufficient iron stores.

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Chapter 7

A randomized controlled trial examining the addition of folic acid to iron supplementation in the treatment of postpartum anemia

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Abstract

Objective: To evaluate the efficacy of adding folic acid to oral iron supplementation in postpartum women with anemia.

Methods: A randomized controlled trial was conducted in the Netherlands between April 8, 2008, and August 31, 2010. A total of 112 postpartum women with anemia (hemoglobin [Hb] < 10.5 g/dL) were randomly allocated to receive 600 mg/day ferrous fumarate plus 1 mg/day folic acid (FFFA group) or 600/day ferrous fumarate alone (FF group) for 4 weeks. Primary outcome measures were Hb and health status (HS). Secondary outcome measures were fatigue, compliance, and adverse reactions.

Results: Intention-to-treat analyses showed no interaction effects on Hb, HS and fatigue scores. The FFFA group showed a steeper increase on serum folate concentration compared with the FF group ($p < 0.0001$). Hb significantly increased over time ($p < 0.0001$). Also, an overall time effect was observed for HS and fatigue, most scores improved. A group effect for the EQ-5D pain and discomfort scale ($p < 0.0001$) and VAS ($p < 0.05$) was observed. The FFFA group reported higher pain scores on the EQ-5D and lower VAS scores compared with the FF group.
Only 50.5% of all women ($n = 46$) ingested all 84 prescribed ferrous fumarate tablets. Approximately 75% of all women reported having at least one symptom resulting from ferrous fumarate use. Constipation caused by ferrous fumarate was significantly associated with non-compliance ($p = 0.014$).

Conclusion: The addition of folic acid to iron supplementation is not beneficial in women with postpartum anemia, as it has no effect on hematologic or HS parameters.

Introduction

Approximately 21% of women in high-income countries experience postpartum anemia, a condition characterized by tiredness, maternal infections, depression, and impairments in mother–child interactions and infant development [1–4]. Treatment of postpartum anemia could, therefore, contribute to maternal health and infant development. Health status (HS) is a multidimensional concept, which refers to self-perceived physical, mental, and social functioning, and can be assessed by standardized questionnaires [5].

For active erythropoiesis to take place, adequate supplies of folate, cobalamin (vitamin B12), and iron are needed [6]. A deficiency in any one of these can reduce erythrocyte production and, subsequently, the numbers of circulating erythrocytes; substantial reduction can result in anemia [6]. Folate and vitamin B12 are both required for the extensive DNA synthesis that accompanies the production of hundreds of billions of new erythrocytes each day [6]. A decrease in vitamin B12 concentration has been observed during pregnancy, but the concentration of the active moiety, holotranscobalamin, remains unchanged [7].

Pregnant women require supplementation with iron and folic acid because of the increase in maternal hematopoiesis, rapidly dividing cells in the fetus, and because of elevated urinary losses of these nutrients [8]. WHO recommends universal daily supplementation with 60 mg/day elemental iron and 400 µg/day folic acid for 6 months during pregnancy and for the first 3 months postpartum to prevent iron-deficiency anemia [9].

The management of postpartum anemia is unclear because of significant variations in treatment and outcome measures [10]. In a randomized controlled trial (RCT) [11], postpartum women with anemia treated with 80 mg/day ferrous iron, with or without 0.35 mg/day folic acid, were compared with placebo. Hematological parameters and subjective health conditions improved significantly in both treatment groups; however, no difference was found between women who did and did not receive folic acid [11]. All women were selected during their third trimester of pregnancy, when their hemoglobin (Hb) levels were above 10 g/dL, and all started treatment after spontaneous delivery, without consideration of their Hb level at that time. In addition, subjective health was determined without the use of a standardized HS questionnaire.

The aim of the present study was to determine whether the addition of folic acid to oral iron supplementation improved Hb and HS in women with postpartum anemia. The effect of these agents on fatigue, compliance with treatment, and adverse reactions was also determined.

Materials en methods

The present RCT was conducted between April 8, 2008, and August 31, 2010, at the Department of Obstetrics and Gynecology, TweeSteden Hospital, Tilburg, in the southern part of the Netherlands. Approval was obtained from the local ethics committee (file number NL21797.028.08). All women received verbal and written information about the study, and provided verbal and written informed consent.

Women were eligible for inclusion if they were 18 years or older, thoroughly understood the Dutch language, and had indications for Hb determination within 48 hours after delivery. Indications included estimated blood loss over 500 mL, delivery by cesarean, manual removal of the placenta, and clinical symptoms of anemia. Women were excluded for the following reasons: Hb less than 6.4 g/dL (because the hospital protocol indicates the need for packed red cell transfusion); addiction to alcohol or drugs; hematological disease; vitamin B12 deficiency (serum vitamin B12 < 100 nmol/L and holotranscobalamin < 20 pmol/L); methotrexate use; and contraindications for folic acid and ferrous fumarate.

Within 48 hours postpartum (T0), maternal venous blood was collected to determine hematological parameters, and HS was measured using the self-reported standardized 36-item Short-Form Health Survey (SF-36), the European Quality of Life questionnaire (EQ-5D), and the Visual Analogue Scale (VAS) of the EQ-5D. Fatigue was measured using the Checklist Individual Strength (CIS).

Anemia was defined, according to Dutch guidelines, as Hb less than 10.5 g/dL [12]. Women were enrolled by random selection of opaque, taped envelopes containing a note reading “ferrous fumarate plus folic acid” (FFFA group) or “ferrous fumarate alone” (FF group). Doctors and the included women were not blinded to allocation as no placebo was used. All included women were prescribed 200 mg ferrous fumarate three times daily for 4 weeks, whereas women in the FFFA group were also prescribed

0.5 mg folic acid twice daily for 4 weeks. Women who did not have anemia (Hb ≥ 10.5 g/dL) were excluded from randomization.

Women were followed up at the outpatient clinic 5 weeks after delivery (T5), at which time hematological parameters and HS were again measured. Compliance with medication was measured by counting the numbers of remaining tablets. Adverse effects were assessed using a list of symptoms that frequently occur after ferrous fumarate or folic acid use. This list was completed by the women themselves during the follow-up appointment.

Blood Hb, erythrocyte mean corpuscular volume, erythrocyte volume fraction (hematocrit), erythrocyte mean corpuscular hemoglobin concentration, erythrocyte mean corpuscular hemoglobin, hemoglobin content in reticulocytes, and total reticulocyte count were analyzed using an Advia 2120i (Siemens Healthcare Diagnostics, Breda, Netherlands) automated cell counter. Total serum iron and total iron binding capacity (TIBC) were measured on an Advia 1650 chemistry analyzer (Siemens Healthcare Diagnostics). Transferrin concentration was measured on a Beckman Coulter Immage 800 immunochemistry analyzer (Beckman Coulter, Mijdrecht, Netherlands). Serum ferritin and folic acid were measured on an Advia Centaur immunoassay system (Siemens Healthcare Diagnositcs). Folic acid levels less than 7 nmol/L were considered indicative of folic acid deficiency.

Iron-deficiency anemia was defined as Hb less than 10.5 g/dL plus mean corpuscular volume less than 80 fL or hemoglobin content in reticulocytes less than 28 pg (1.74 fmol) [13]. Hb, measured as mmol/L was converted to g/L by multiplying by 16.115, whereas Hb measured as g/L was converted to mmol/L by multiplying by 0.062054. Iron saturation was calculated as (serum iron/ total iron binding capacity) x 100%.

The SF-36 is a generic questionnaire that was chosen because it covers all HS domains, and is often used in determining HS in postpartum women. Each of the 36 items has a scoring range from 0 to 100, with higher scores representing better levels of functioning [14]. In addition, the SF-36 provides a physical component summary and a mental component summary.

The EQ-5D is a generic HS questionnaire containing five items, each with a scoring range from 1 to 3, with higher scores representing worse functioning [15]. Included

in the EQ-5D is the VAS, which represents a global evaluation of health on a scale ranging from 0 (worst imaginable health status) to 100 (best imaginable health status). This questionnaire was chosen because of its simplicity and rapid completion time. Both the SF-36 and EQ-5D have demonstrated good psychometric properties in postpartum women [16].

The CIS is a multidimensional scale that quantifies subjective fatigue and related behavioral aspects [17]. This questionnaire was chosen because fatigue is a symptom of anemia. Each of the 20 items is scored from 1 to 7, with higher scores indicating greater fatigue. CIS is a reliable and valid tool in people with chronic fatigue syndrome as well as in healthy populations [18].

The primary outcome measures were Hb and HS increases after 4 weeks of treatment. Secondary outcome measures were fatigue, compliance, and adverse reactions.

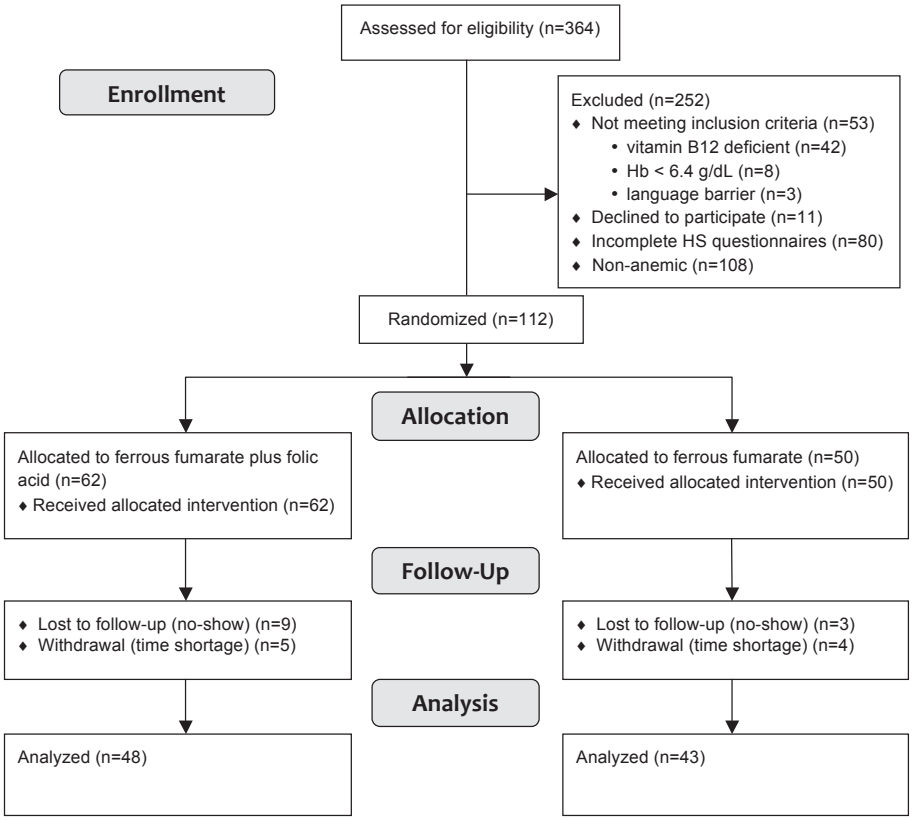
Sample size calculation was based on the hypothesis that increases in Hb concentration and HS over time would be greater in the FFFA than in the FF group. A priori sample size calculation was carried out using analysis of variance for repeated measures by the G-power 3.1 calculator [19]. Assuming an effect size of 0.5, with an α-error of 0.05 and a power of 80%, a total sample size of 26 participants was required. To be able to undertake sub-analyses, the sample size was expanded to include 112 women with anemia.

All statistical analyses were conducted using SPSS 15.0 (IBM, Armonk, NY, USA). Baseline characteristics, compliance, and adverse effects in the two groups were assessed using independent sample T tests or Chi square tests. All analyses were conducted according to intention-to-treat principles. ANOVA for repeated measures was used to compare the group who received folic acid with the group who received folic acid and oral iron supplementation on hematological parameters and HS and fatigue scores across time, with correction for the number of tests using the Bonferroni rule. All results are reported as mean $\pm$ standard deviation or percentage (%). $p < 0.05$ was considered statistically significant.

Results

The flow of participants through the study is shown in accordance with CONSORT criteria (Figure 1). Of the 364 women screened, 53 did not meet the inclusion criteria, 42 were excluded owing to vitamin B12 deficiency, eight were excluded because Hb was less than 6.4 g/dL, and three were excluded owing to language constraints. Eleven women declined to participate. Eighty women did not complete the baseline HS questionnaires for unknown reasons, and were therefore excluded, as were 108 women who did not have anemia (Hb ≥ 10.5 g/dL). As a result, 112 women were randomly allocated between the groups. Of these, 91 women were available for analyses because 12 were lost to follow up, and nine withdrew.

Figure 1 Flow chart of patients



The demographic and clinical characteristics of the participants by treatment group are shown in Table 1. No relevant differences among the groups were detected at baseline. Each group included eight women with a serum folate deficiency at baseline (p = 0.64). Iron-deficiency anemia was present in 18 women in the FFFA group and 21 in the FF group (29% vs 42%, p = 0.15).

Table 1 Patient demographic and clinical characteristics at baseline (To) [a]

	Ferrous fumarate plus folic acid (n=62)	Ferrous fumarate (n=50)
Age at entry (years)	31.0 ± 4.7	30.1 ± 4.5
BMI before pregnancy (kg/m²)	25.2 ± 4.7	25.3 ± 6.2
Caucasian	55 (88.7)	42 (84)
Highest education		
Lower	3 (5.2)	3 (6.1)
Medium	29 (50)	27 (55.1)
High	26 (44.8)	19 (38.8)
Smoking	9 (14.5)	6 (12.2)
Multivitamin or FA use	30 (48.4)	18 (36)
Parity at baseline	1.6 ± 0.9	1.4 ± 0.7
Gestational age at delivery (weeks)	40.0 ±1.6	40.0 ± 1.6
Delivery method		
Vaginal	40 (64.5)	30 (60.0)
Cesarean section	22 (35.5)	20 (40.0)
Estimated blood loss (ml)	834 ± 436	811 ± 395
Infant feeding		
Breastfeeding	36 (58.1)	34 (68)
Bottle (formula) feeding	26 (41.9)	16 (32)
Serum folate deficiency	8 (12.9)	8 (16)
Iron deficiency anemia	18 (29.0)	21 (42.0)

Abbreviations: BMI = Body Mass Index (calculated as weight in kilograms divided by the square of height in meters), FA = folic acid.

[a] Values are given as mean ± SD or number (percentage).

Intention-to-treat analyses on hematologic parameters showed no interaction effects, except for serum folate concentration (p < 0.0001, Table 2). The FFFA group showed a steeper increase on serum folate concentration compared with the FF group. Significant effects of time were found with regard to Hb (p < 0.0001), hematocrit (p < 0.0001), mean corpuscular volume (p < 0.0001), mean corpuscular hemoglobin (p < 0.008), mean corpuscular hemoglobin concentration (p < 0.0001), iron saturation (p < 0.0001), and TIBC (p < 0.0001). Hb, hematocrit, mean corpuscular volume, and iron saturation increased over time, while mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and TIBC decreased. No group effect was observed.

Table 2 Hematology results at baseline (T0) and after 4 weeks of treatment (T5) [a]

	Ferrous Fumarate plus Folic Acid (FFFA)		Ferrous Fumarate (FF)	
	T0	T5	T0	T5
Hemoglobin, g/dL [b]	9.2 ± 0.9	12.4 ± 1.0	9.2 ± 0.9	12.2 ± 1.1
Hematocrit, % [b]	0.27 ± 0.03	0.38 ± 0.03	0.27 ± 0.03	0.37 ± 0.03
Mean corpuscular volume, fL [b]	84.3 ± 5.4	85.4 ± 5.7	82.7 ± 6.1	83.9 ± 5.4
Mean corpuscular hemoglobin, fmol [b]	1.76 ± 0.14	1.74 ± 0.14	1.73 ± 0.16	1.70 ± 0.13
Mean corpuscular hemoglobin concentration, mmol/L [b]	20.9 ± 0.6	20.5 ± 0.7	21.0 ± 0.6	20.3 ± 0.7
Serum Iron, µmol/L	11.7 ± 5.7	14.6 ± 8.0	12.2 ± 6.4	13.3 ± 10.4
Iron saturation, % [b]	15.8 ± 8.1	22.8 ± 13.2	15.8 ± 8.7	20.9 ± 16.5
Total iron binding capacity, µmol/L [b]	77.2 ± 14.8	64.9 ± 8.1	78.0 ± 11.1	66.3 ± 7.7
Ferritin, µg/L	32.1 ± 35.7	23.9 ± 9.0	22.5 ± 17.1	24.0 ± 12.3
Transferrin, g/L	3.7 ± 0.7	3.1 ± 0.4	3.7 ± 0.6	3.2 ± 0.5
Reticulocyte hemoglobin content, pg	1.87 ± 0.17	1.88 ± 0.18	1.86 ± 0.21	1.84 ± 0.18
Folic acid, nmol/l [c]	15.3 ± 8.7	34.1 ± 13.3	14.9 ± 11.1	19.4 ± 11.8

[a] Values are given as mean ± SD

[b] Repeated measures ANOVA: significant effect of time ($p < 0.0001$)

[c] Repeated measures ANOVA: interaction effect between FFFA and FF group ($p < 0.0001$)

Note: There were no significant differences between the FFFA and FF group on the other variables

In addition, intention-to-treat analyses on the SF-36, EQ-5D, and CIS scores showed no interaction effects (Table 3). However, an overall time effect was observed with regard to the SF-36 subscales physical functioning, social functioning, role physical, mental health, vitality, bodily pain, PCS, MCS, and total scores ($p < 0.0001$), the EQ-5D subscales mobility, self care, daily activities, pain and discomfort, total scores, and VAS ($p < 0.0001$) and the CIS subscales subjective fatigue, motivation, and activity, and total scores ($p < 0.0001$). All scores improved. Also, a group effect for the EQ-5D pain and discomfort scale ($p < 0.0001$) and VAS ($p < 0.05$) was observed. The FFFA group reported higher pain scores on the EQ-5D and lower VAS scores compared with the FF group.

At 5 weeks postpartum, 72.3% (n = 34) of the women in the FFFA group and 66.7% (n = 28) of those in the FF group reached non-anemic Hb levels (> 12.0 g/dL) ($p = 0.56$). When women in the two groups were stratified by baseline severe (Hb 6.4–8.0 g/dL, n = 12) and moderate (Hb 8.0–10.5 g/dL, n = 77) anemia, no significant between-group differences were found in the percentage of women with severe ($p = 0.68$) and moderate ($p = 0.93$) anemia attaining non-anemic Hb levels (Figure 2).

Table 3 Health status by group at baseline (T0) and after 4 weeks of treatment (T5) [a]

	Ferrous Fumarate plus Folic Acid		Ferrous Fumarate	
	T0	T5	T0	T5
SF-36				
Physical functioning [b]	39.8 ± 32.7	80.0 ± 18.7	43.4 ± 36.5	84.2 ± 16.2
Social functioning [b]	64.3 ± 26.7	85.4 ± 19.2	71.5 ± 24.1	84.6 ± 23.3
Role physical [b]	29.8 ± 38.9	64.9 ± 43.5	39.5 ± 38.3	74.4 ± 38.4
Role emotional	86.5 ± 33.8	87.2 ± 32.3	84.1 ± 31.4	96.0 ± 51.2
Mental health [b]	78.4 ± 15.5	86.9 ± 11.3	79.5 ± 11.7	85.5 ± 11.0
Vitality [b]	52.8 ± 22.2	65.5 ± 15.7	56.9 ± 18.4	66.8 ± 15.0
Bodily pain [b]	56.0 ± 30.1	81.5 ± 20.4	65.0 ± 28.0	87.2 ± 19.4
General health	79.5 ± 15.3	79.7 ± 16.3	80.8 ± 11.6	80.3 ± 11.4
Health change	45.3 ± 21.0	45.8 ± 22.1	44.2 ± 14.3	47.1 ± 14.6
Physical component summary [b]	50.8 ± 20.8	76.5 ± 20.2	57.6 ± 22.0	81.7 ± 17.2
Mental component summary [b]	70.1 ± 18.5	81.5 ± 15.7	73.1 ± 14.5	84.0 ± 18.3
Total [b]	58.8 ± 16.6	75.3 ± 15.2	63.2 ± 15.4	78.7 ± 15.1
EQ-5D				
Mobility [b]	1.96 ± 0.71	1.17 ± 0.38	2.02 ± 0.77	1.07 ± 0.26
Selfcare [b]	1.69 ± 0.62	1.04 ± 0.20	1.77 ± 0.72	1.00 ± 0.00
Daily activities [b]	2.21 ± 0.68	1.38 ± 0.57	2.16 ± 0.81	1.28 ± 0.50
Pain and discomfort [b,c]	1.94 ± 0.38	1.52 ± 0.55	1.70 ± 0.51	1.23 ± 0.43
Anxiety and depression	1.17 ± 0.38	1.13 ± 0.33	1.16 ± 0.37	1.09 ± 0.29
Total [b]	8.94 ± 2.05	6.23 ± 1.49	8.81 ± 2.49	5.67 ± 0.99
Visual Analogue Scale [b,d]	65.7 ± 16.2	76.9 ± 12.4	71.1 ± 13.2	81.8 ± 9.3
Checklist Individual Strength				
Subjective fatigue [b]	36.9 ± 12.4	26.6 ± 11.5	33.3 ± 12.4	25.8 ± 10.0
Reduced motivation [b]	13.1 ± 6.1	8.1 ± 3.3	13.1 ± 5.4	9.2 ± 4.0
Reduced activity [b]	12.2 ± 5.6	7.8 ± 4.4	11.4 ± 5.5	8.4 ± 3.6
Reduced concentration	15.8 ± 8.1	13.2 ± 8.0	14.4 ± 6.9	13.6 ± 7.3
Total [b]	77.7 ± 27.5	55.8 ± 21.8	71.6 ± 25.0	57.1 ± 18.7

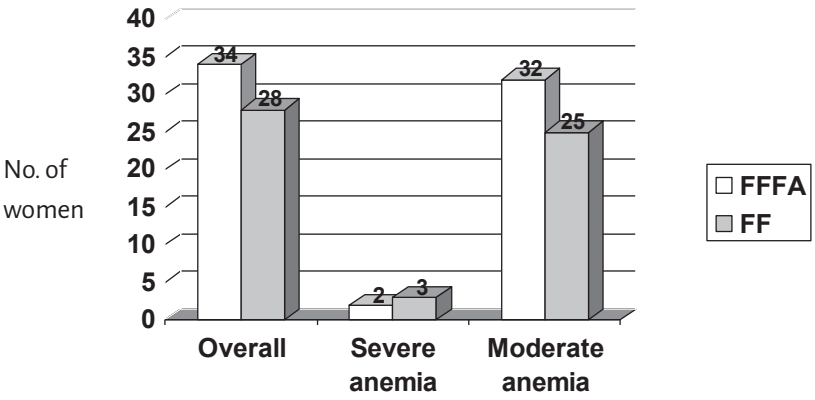
[a] Values are given as mean ± SD
[b] Repeated measures ANOVA: significant effect of time ($p < 0.0001$)
[c] Repeated measures ANOVA: significant group effect ($p < 0.0001$)
[d] Repeated measures ANOVA: significant group effect ($p < 0.05$)
Note: There were no effects with regard to the other variables

None of the women experienced serious adverse effects. However, 74.7% (n = 68) of all women, 77.1% in the FFFA (n = 37), and 72.1% in the FA group (n = 31) (p = 0.58) reported having at least one symptom as a result of ferrous fumarate use. The most common of these symptoms was colored feces and constipation, which were reported by 64.8% (n = 59) and 38.5% (n = 35) of these women, respectively. Only two women (4.3%) in the FFFA group reported skin rash as a result of folic acid use.

Of the women in both groups, 50.5% (n = 46) ingested all 84 prescribed ferrous

fumarate tablets and 76.7% (n = 69) ingested more than 75% (> 63 tablets). Of the women in the folic acid group, 62.5% (n = 30) ingested all 56 prescribed folic acid tablets, and 79.2% (n = 38) ingested more than 75% (> 42 tablets). Constipation caused by ferrous fumarate was associated with non-compliance. Women without constipation ingested 20 or more ferrous fumarate tablets than women with constipation (p = 0.014).No association was found between folic acid compliance and skin rash (p = 0.28).

Figure 2 Number of women per group with hemoglobin over 12.0 g/dL at 5 weeks postpartum



Discussion

In the present RCT, the addition of folic acid to iron supplementation did not confer additional benefit, as shown by Hb concentration and HS in women with postpartum anemia. Fatigue scores were also not affected by folic acid addition. Approximately 75% of the women in this trial reported having at least one symptom arising from ferrous fumarate use, with constipation caused by ferrous fumarate significantly associated with non-compliance.

An earlier RCT also found no difference in hematological parameters and subjective health conditions between postpartum women who did and did not receive folic acid, but probably also included women without postpartum anemia [11]. In contrast, an

RCT in anemic pregnant women in Mexico found that Hb levels were higher after iron and folic acid supplementation than after iron supplementation alone; those results were independent of serum folate concentrations [20]. The differences in diet and socioeconomic status between Mexican and European populations make it difficult to compare these findings with those of the present study.

Approximately 75% of all the women in this trial experienced an adverse effect of ferrous fumarate, which is higher than the 56% reported in a study involving pregnant women [21]. This difference may be attributable to the higher ferrous fumarate dose used in the present study, as adverse effects are dose related [22]. Iron dosage in the present study, however, was consistent with the recommended dosage of 100–200 mg/day ferrous iron in women with slight-to-moderate postpartum anemia [23]. Non-compliance owing to gastrointestinal adverse effects is consistent with previous findings [22].

Although the study participants were randomized between the two treatment arms, the results of randomization were not blinded, and therefore may have influenced study outcomes. Serum folic acid concentration, however, increased significantly over time in the FFFA group compared with the FF group, suggesting that the lack of placebo did not alter the results substantially. Although central randomization is generally recommended, participants in the present study were randomized using concealed opaque envelopes. There is no evidence, however, that the use of these envelopes differed from central randomization [24]. Hematology outcomes were only measured up to 5 weeks after delivery. These outcomes may have been different after a longer follow-up period. As erythroblast maturation takes 5–7 days, however, any between-group difference in Hb concentrations would have been detected after 5 weeks [25].

Because this study included women of different ages, educational levels, parity, and modes of delivery, the results are applicable in daily medical practice. The addition of folic acid to iron supplementation does not benefit women with postpartum anemia, and is not required in daily practice in high-income countries. The present study was conducted in the Netherlands, and most women were white with western dietary habits; therefore, these results cannot be extrapolated to low-income countries.

In conclusion, the addition of folic acid to iron supplementation does not improve Hb, HS, and fatigue in women with postpartum anemia. Oral iron supplementation was associated with a high rate of adverse effects, such as constipation. Constipation was significantly associated with non-compliance.

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Chapter 8

General discussion

General discussion

Despite the fact that micronutrient deficiency is a common problem [1, 2], which was found to be associated with impaired health status (HS) and quality of life (QOL), and increased fatigue [3-7], the impact of micronutrient deficiency on maternal HS and fatigue is a neglected topic. Therefore, this thesis examined QOL and HS in postpartum women, and the impact of postpartum micronutrient status on maternal HS and fatigue. We examined anemia, iron, folic acid, vitamin B12, and vitamin D in association with HS and fatigue in postpartum women.

We showed in our systematic review (chapter 2) that studies concerning the association of micronutrient deficiency with postpartum HS and QOL are lacking. Since anemia and vitamin D deficiency were found to be associated with impaired HS [5, 7] and increased fatigue [3, 4, 6] in the current literature, we examined whether this association also existed in postpartum women. We compared postpartum HS and fatigue between anemic and non-anemic women, and women with sufficient and insufficient vitamin D levels.

Surprisingly, no differences were observed in HS and fatigue scores between postpartum women with or without anemia (chapter 3). To our knowledge, this is the first study to compare all domains of HS and fatigue (physical, mental, and social functioning) in postpartum women with and without anemia. In agreement with an earlier study, we found that HS and fatigue scores improved over time in all groups and were not associated with hemoglobin (Hb) level [8].

The results of our study may be explained by the fact that postpartum anemia was based on Hb level within 48 hours after delivery, when a low Hb level can be physiological. Hb level decrease during pregnancy is caused by hypervolemia and hemodilution [9, 10]. Postpartum, increased diureses eliminates the excess plasma volume, leading to hemoconcentration and an increase of Hb concentration from the third postpartum day to prepartum values at one week postpartum and to normal values at four weeks postpartum [10]. Recently, no improvement of HS and fatigue were found after red blood cell transfusion in severe acute postpartum anemic women (Hb 4.8–7.9 g/dL) compared with non-intervention [11]. All included women had ≥ 1000 ml blood loss and/or a decrease in Hb concentration of ≥ 1.9 g/dL. In this study, anemia was based on Hb level within 24 hours after peripartum

hemorrhage. Therefore, we conclude that HS and fatigue are not associated with anemia based on Hb level.

Another explanation for the fact that we did not find a difference in HS and fatigue between postpartum women with or without anemia, may be that the vast majority of our anemic postpartum women were not iron deficient (chapter 6). That means that the cause of anemia in our postpartum women was not iron deficiency, but another etiology. Besides hemodilution [9, 10] or peripartum hemorrhage [9, 11], postpartum anemia can also be due to deficiencies in micronutrients for erythropoiesis such as iron, folic acid, or vitamin B12 [9, 12]. In the current literature, iron deficiency (anemia) in particular, seems to be the major component associated with decreased physical and work capacity [13-15], reduced cognition [16, 17], and decreased HS [7]. We believe that iron deficiency anemia postpartum may result in an impaired HS and fatigue. As far as we know, there are no data comparing HS and fatigue between postpartum anemic women with or without iron deficiency. In only one RCT the difference in cognition, mood, and behavior among postpartum women with iron deficiency anemia and non-anemic women was examined between 10 weeks and 9 months postpartum [18]. The iron deficient anemic women were randomized between vitamin C and folic acid supplementation (placebo group), and oral iron, vitamin C, and folic acid supplementation (iron supplementation group). After treatment, significantly more women in the placebo group than in the iron supplementation group were still anemic. At baseline, no significant differences in cognition, mood and behavior were observed between iron deficient anemic women compared with non-anemic women. After treatment, cognition, mood, and behavior improved in the iron supplemented group when compared to the placebo and non-anemic group. However, this study was performed among poor women in South Africa, who consumed < 75% of estimated daily requirements for nutrient intake. Therefore, these results cannot be extrapolated to postpartum anemic women in The Netherlands, as it is a high-income country with other dietary habits and nutritional status. Also, even though there were no significant differences in dietary intake patterns between the groups, vitamin C and folic acid level were not determined between the groups. Therefore, the observed improvements in the iron supplemented group could also be explained by a reduced vitamin C and folic acid before treatment. In conclusion, this placebo controlled RCT has a number of weaknesses, making it not applicable for daily practice in The Netherlands. Additional studies are needed to compare all three domains of HS (physical, mental, and social), multidimensional fatigue scores,

cognition, mood, and behavior among postpartum women with iron deficiency anemia before and after iron supplementation or placebo treatment.

The existing literature has shown an association of impaired HS and increased fatigue with vitamin D deficiency [3-5]. In this thesis, HS and fatigue were not different among postpartum women with sufficient and insufficient vitamin D levels (chapter 4). These findings can be explained by the influence of other factors on HS and fatigue in the postpartum period, such as cesarean section (chapter 2) or exhaustion caused by infant crying [19]. Despite the fact that a similar prevalence of insufficient vitamin D levels among lactating and bottle feeding women was found (chapter 4), we believe that vitamin D supplementation should only be reserved for lactating postpartum women, as was recommended by international guidelines [20, 21] because the newborn relies on vitamin D supply from maternal breast milk.

We have already shown that anemia based on Hb level was not related to postpartum HS and fatigue, but we also examined the role of iron, folic acid, and vitamin B12 levels in postpartum women. We found that even though vitamin B12 deficiency was highly prevalent directly postpartum, based on serum vitamin B12 and holotranscobalamine (holoTC), this deficiency spontaneously resolved at 5 weeks postpartum (chapter 5). The fraction of active vitamin B12 (holoTC/total vitamin B12) was significantly higher in vitamin B12 deficient women at both time points and across time (chapter 5), suggesting that a shift occurs towards the metabolic active vitamin B12 (holoTC) in women with insufficient available total vitamin B12. Our results confirm the hypothesis that the changes of vitamin B12 levels during pregnancy and postpartum are physiologic and based on redistribution [22, 23]. In our opinion, screening for vitamin B12 deficiency is unnecessary in postpartum women without risk factors for true vitamin B12 deficiency. Postpartum women do not need vitamin B12 supplementation, since vitamin B12 deficiency spontaneously resolves.

International guidelines regarding treatment of postpartum anemia do not discriminate between the etiologies of anemia. Based on Hb concentration, these guidelines recommend oral iron supplementation for mild to moderate postpartum anemia [24-26] because of its low cost and ease of use [27]. Despite the fact that oral iron supplementation seems harmless, many postpartum women experience adverse effects such as constipation, which results in non-compliance (chapter 7). Since, iron absorption from the gut is inhibited if iron stores are sufficient [28], iron

supplementation could result in overtreatment in postpartum women without iron deficiency anemia. We examined the prevalence of iron deficiency in postpartum anemic women by using mean corpuscular volume (MCV) and reticulocyte hemoglobin content (CHr), and found that only 36% of the women were iron deficient (chapter 6). There was a significant Hb concentration increase in all anemic and non-anemic women over time. No difference in Hb concentration increase was observed between anemic women with and without iron deficiency. However, anemic women with iron deficiency showed a significant improvement towards normalization of the MCV and CHr parameters, while the anemic women without iron deficiency did not show a significant increase in the MCV and CHr parameters. These results show that only iron deficient anemic women benefit from oral iron supplementation. In order to prevent overtreatment with oral iron supplementation in postpartum anemic women, MCV or CHr measurement in addition to Hb concentration is needed.

Folic acid in addition to oral iron supplementation is recommended and applied in order to prevent and treat postpartum anemia [2, 27, 29, 30]. We showed in our RCT that the addition of folic acid to oral iron supplementation is not beneficial in the treatment of postpartum anemia, as it has no effect on hematological, HS and fatigue parameters (chapter 7). A RCT performed by Mará et al. found no difference in hematological parameters and subjective health conditions between postpartum women who did and did not receive folic acid [31]. However, the study probably also included postpartum women without anemia and subjective health was determined without the use of a standardized HS questionnaire. In contrast, Juarez-Vazques et al. performed a RCT in anemic pregnant women in Mexico and found that Hb levels were higher after iron and folic acid supplementation than after iron supplementation alone [32]. However, the study was performed in pregnant women instead of postpartum women and the difference in diet and socioeconomic status between Mexican and European populations makes it impossible to extrapolate the results of these studies to postpartum anemic women in The Netherlands. The strength of our study is the heterogeneous population, including women of different ages, educational levels, parity, and modes of delivery. Therefore, the results of our study are applicable in daily medical practice in The Netherlands. We conclude that the addition of folic acid to oral iron supplementation is not required in high-income countries. As a result, the guidelines should be changed to reflect our findings. This will reduce health care costs.

Clinical implications and future perspectives

Even though vitamin D insufficiency and anemia are highly prevalent in postpartum women, we showed that they do not influence maternal HS and fatigue. In accordance with the international guidelines, we recommend vitamin D supplementation in lactating women because the newborn relies on vitamin D supply from maternal breast milk [20, 21].

The association of treatment of postpartum anemia and the impact on maternal HS and fatigue has not been fully clarified. In this thesis, we have contributed to this knowledge by concluding that the addition of folic acid to oral iron supplementation is not required in high-income countries. As a result, the guidelines should be changed to reflect our findings. This will reduce health care costs.

Recently, it was concluded that red blood cell transfusion has to be restricted to postpartum anemic women with severe anemic symptoms, severe comorbidities, or circulatory instability, as it does not improve maternal HS and fatigue [11]. Postpartum anemia based on Hb alone was not associated with maternal HS and fatigue. The current guidelines recommend iron supplementation in postpartum anemic women based on Hb level, but our study implicates that this could lead to overtreatment. We found that only 36% of the postpartum anemic women were iron deficient. These women probably have the most benefit from iron supplementation. After oral iron supplementation, iron status improved in our iron deficient anemic women. Also, previous studies showed that iron deficiency with or without anemia was associated with decreased physical and work capacity [13-15], reduced cognition [16, 17], and decreased HS [7] in the general population.

Based on our study we believe that iron supplementation should be reserved for postpartum anemic women with iron deficiency. To examine this hypothesis, a randomized controlled trial is needed to compare all three domains of HS (physical, mental, and social), multidimensional fatigue scores, cognition, mood, and behavior, among postpartum women with iron deficiency anemia before and after iron supplementation or placebo treatment. MCV and CHr should be used to define iron deficiency.

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Chapter 9

Summary

Samenvatting

Summary

Chapter 1

Chapter 1 provides a general introduction on quality of life (QOL), health status (HS) and fatigue in relation to postpartum micronutrient deficiency and anemia. In addition, the research questions of this thesis are outlined.

During pregnancy, maternal physiological changes and fetal demands for growth and development increase the requirements for micronutrients. Micronutrient deficiency is a common problem in both developing and developed countries. Iron, folic acid, and vitamin B12 are required for the production of red blood cells. Deficiency of one of these micronutrients can lead to anemia. Anemia and vitamin D deficiency can lead to fatigue and reduced HS and/or QOL. So far, these associations have not been studied in postpartum women.

Health care is becoming more and more patient centered. Therefore, patient-reported outcomes become increasingly important. In this thesis, we investigated whether anemia and vitamin D deficiency are associated with reduced HS and increased fatigue in postpartum women. We also investigated the iron status and the effect of folic acid supplementation in anemic postpartum women. Finally, the course of vitamin B12 deficiency in the first postpartum weeks was investigated.

Chapter 2

The results are described of a systematic review regarding QOL and HS in postpartum women. Only studies in which at least the physical, mental and social domains were described, were included in the review (n = 66). The aspects that were most studied in postpartum women were: urine incontinence, cesarean section, human immunodeficiency virus (HIV), and depression. In none of the studies a control group of healthy fertile women was included, hence results are difficult to interpret.

Regarding studies related to micronutrient deficiency in postpartum women, only two randomized controlled trials could be included. These studies examined anemia in postpartum women. Due to differences in treatment and hemoglobin (Hb) cutoff values, results could not be compared.

Chapter 3

HS and fatigue were compared between women with and without postpartum anemia in this prospective cohort study of postpartum women. The anemic women (n = 112) were treated with oral iron supplementation with or without folic acid. Non-

anemic women (n = 108) received no treatment and were prospectively followed during the study. After adjustment for confounders (including cesarean section), no difference was found in HS and fatigue between the anemic and non-anemic postpartum women. In all women HS and fatigue scores improved significantly over time ($p < 0.0001$). Linear regression analysis showed no association of anemia and the amount of blood loss with any of the HS and fatigue scores within 48 hours and at 5 weeks postpartum.
It was concluded that there was no difference in HS and fatigue between anemic and non-anemic postpartum women. Overall, HS and fatigue improved over time in all postpartum women.

Chapter 4
In this chapter the prevalence of postpartum vitamin D sufficiency and insufficiency between breastfeeding and bottle feeding with their associated HS and fatigue are described. Vitamin D insufficiency was not different between breastfeeding and bottle feeding groups (57% vs. 64%, $p = 0.46$). There were no significant differences in HS and fatigue among breastfeeding women with or without vitamin D insufficiency. When bottle feeding, women with insufficient vitamin D scored significantly worse on the general health scale ($p = 0.035$). This finding is probably due to chance or the effect of multiple testing, because this difference was not found in breastfeeding women.
In conclusion, maternal vitamin D status is not associated with breastfeeding or bottle feeding, and HS and fatigue are not associated with maternal vitamin D status.

Chapter 5
The prevalence of vitamin B12 deficiency postpartum based on total vitamin B12 and the metabolic active vitamin B12 (holotranscobalamine) was described in this chapter. Also, the hypothesis that a shift occurs towards holotranscobalamin in postpartum women with insufficient available total vitamin B12 was examined. In 171 postpartum women, the fraction of active vitamin B12 (holotranscobalamin/ total vitamin B12) was compared between vitamin B12 deficiency and not deficiency. Vitamin B12 deficiency showed a spontaneous improvement of 60-75% within 48 hours postpartum to 6-10% at 5 weeks postpartum. The fraction of active vitamin B12 was significantly higher in vitamin B12 deficient women compared to women who were not vitamin B12 deficient ($p < 0.0001$).

In conclusion, there appears to be a shift in the direction of the metabolic active holotranscobalamine in women with insufficient available total vitamin B12. These results suggest that the changes of postpartum vitamin B12 are physiologically and are explained by redistribution.

Chapter 6

In this chapter the usability of mean corpuscular volume (MCV) and reticulocyte hemoglobin content (CHr) to diagnose iron deficiency in postpartum anemic women was described. In a prospective cohort, anemic women were subdivided in microcytic (MCV < 80 fL, n = 30) and normocytic (MCV ≥ 80 fL, n = 85), or low CHr (< 28 pg, n = 30) and normal CHr (≥ 28 pg, n = 75). Only 36% of anemic women were iron deficient. All anemic women were treated with ferrous fumarate with or without folic acid for 4 weeks. No difference in Hb level increase was observed between the iron deficient and non-iron deficient groups. Women with iron deficiency showed significant improvement in the direction of normalization of MCV and CHr parameters, while non-iron deficient women did not show this increase.
In conclusion, a combination of Hb with MCV or CHr can identify an actual iron deficiency in postpartum anemic women.

Chapter 7

In this chapter the results of a randomized controlled trial are described in which 112 postpartum women with anemia were randomly assigned to receive either 600 mg ferrous fumarate plus 1 mg folic acid per day (n = 48) or 600 mg/day ferrous fumarate alone (n = 43) for 4 weeks. After treatment, no differences were observed in Hb level, HS, and fatigue between the groups. About 75% of all women reported at least one adverse reaction due to ferrous fumarate use. Constipation was significantly associated with discontinuation of ferrous fumarate intake (p = 0.014).
In conclusion, the addition of folic acid to oral iron supplementation is not beneficial in the treatment of postpartum anemia, as it has no effect on hematologic parameters, HS and fatigue.

Chapter 8

In chapter 8, the general discussion, conclusions and clinical implications of this thesis are displayed. The role of vitamin D, anemia, iron, folic acid and vitamin B12 in association with HS and fatigue are described.

Vitamin D insufficiency occurs in approximately 60% of postpartum women and is not associated with HS, fatigue, and infant feeding method. Because the newborn relies on vitamin D supply from maternal breast milk, vitamin D supplementation should be used in lactating women.

Postpartum anemia based on Hb level alone, is not associated with HS and fatigue. The treatment of postpartum anemia generally consists of oral iron supplementation with or without the addition of folic acid. However, the addition of folic acid to the supplementation of oral iron in the treatment of postpartum anemia is not beneficial with respect to Hb level, HS, and fatigue in developed countries. In addition, only 36% of postpartum anemic women have an iron deficiency. To avoid overtreatment and unnecessary side effects, iron supplementation should be reserved for postpartum anemic women with iron deficiency. A combination of Hb with MCV or CHr should be used to diagnose iron deficiency anemia postpartum.

Vitamin B12 deficiency is common immediately postpartum, but spontaneously disappear five weeks postpartum. This change is physiologically and due to redistribution. Postpartum women without risk factors or manifestations of an actual vitamin B12 deficiency do not need vitamin B12 supplementation.

Samenvatting

Hoofdstuk 1

Hoofdstuk 1 geeft een algemene inleiding over kwaliteit van leven, gezondheidsstatus en vermoeidheid in relatie tot postpartum micronutriënten deficiëntie en anemie. Daarnaast wordt een overzicht gegeven van de onderzoeksvragen die in dit proefschrift worden onderzocht.

Tijdens de zwangerschap ontstaat een toegenomen behoefte aan micronutriënten die noodzakelijk zijn om te voldoen aan de fysiologische maternale veranderingen en de foetale groei en ontwikkeling. Micronutriënten deficiëntie is een veel voorkomend probleem in zowel ontwikkelingslanden als ontwikkelde landen. Voor de aanmaak van rode bloedcellen zijn ijzer, foliumzuur en vitamine B12 nodig. Tekort aan één van deze micronutriënten kan leiden tot anemie. Anemie en tekort aan vitamine D kunnen leiden tot vermoeidheid en een vermindering van gezondheidsstatus en/of kwaliteit van leven. Deze associaties zijn bij vrouwen postpartum nooit eerder onderzocht.

Patiënt gerichtheid in de gezondheidszorg staat steeds meer centraal. Hierdoor worden patiënt-gerapporteerde uitkomsten zoals kwaliteit van leven, gezondheidsstatus en vermoeidheid steeds belangrijker. In dit proefschrift onderzochten we of anemie en tekort aan vitamine D geassocieerd zijn met een verminderde gezondheidsstatus en een toegenomen vermoeidheid bij postpartum vrouwen. Tevens onderzochten we de ijzerstatus en het effect van foliumzuursuppletie bij anemische vrouwen postpartum. Tot slot werd het beloop van vitamine B12 deficiëntie in de eerste weken postpartum onderzocht.

Hoofdstuk 2

In hoofdstuk 2 worden de resultaten beschreven van een systematisch literatuuroverzicht over de kwaliteit van leven en de gezondheidsstatus van postpartum vrouwen. Enkel studies waarin ten minste de fysieke, mentale en sociale domeinen waren beschreven, werden geïncludeerd in de review (n = 66). De aspecten die het meest waren onderzocht bij postpartum vrouwen betroffen: incontinentie, sectio caesarea, humaan immunodeficiëntie virus (HIV) dragerschap en depressie. In geen van de studies werd een controlegroep met gezonde vruchtbare vrouwen geïncludeerd, waardoor de resultaten lastig te interpreteren zijn. Ten aanzien van studies met betrekking tot micronutriënten deficiëntie bij postpartum vrouwen, konden slechts twee gerandomiseerde gecontroleerde studies worden geïncludeerd. Deze studies onderzochten het effect van de behandeling van postpartum anemie.

Door verschillen in behandeling en in hemoglobine afkapwaarden konden de resultaten niet worden vergeleken.

Hoofdstuk 3

In hoofdstuk 3 worden de resultaten beschreven van een prospectieve cohort studie bij postpartum vrouwen. Gezondheidsstatus en vermoeidheid werden vergeleken tussen vrouwen met en zonder postpartum anemie. De anemische vrouwen (n = 112) werden behandeld met orale ijzer suppletie met of zonder foliumzuur. Niet-anemische vrouwen (n = 108) werden niet behandeld en werden prospectief vervolgd tijdens de studie. Na correctie voor confounders (inclusief sectio caesarea) werd geen verschil gevonden in gezondheidsstatus en vermoeidheid tussen de anemische en niet-anemische postpartum vrouwen. Bij alle vrouwen verbeterden de gezondheidsstatus en vermoeidheid scores aanzienlijk na verloop van tijd ($p < 0.0001$). Lineaire regressie analyse toonde geen associatie van anemie en de hoeveelheid bloedverlies met de scores van de gezondheidsstatus- en vermoeidheidschalen binnen 48 uur en bij 5 weken na de bevalling.

Kortom, er werd geen verschil gezien in gezondheidsstatus en vermoeidheid tussen anemische en niet-anemische vrouwen. Alle vrouwen lieten duidelijke verbetering zien tijdens de eerste weken na de bevalling.

Hoofdstuk 4

In hoofdstuk 4 wordt de prevalentie beschreven van postpartum vitamine D sufficiëntie en insufficiëntie tussen vrouwen die borstvoeding en flesvoeding geven met de bijbehorende gezondheidsstatus en vermoeidheid. Vitamine D insufficiëntie bleek niet verschillend tussen de groepen die borstvoeding en flesvoeding gaven (57% versus 64%, $p = 0.46$). Er waren geen significante verschillen met betrekking tot gezondheidsstatus en vermoeidheid tussen vrouwen met of zonder vitamine D sufficiëntie die borstvoeding gaven. Bij de vrouwen die flesvoeding gaven werd significant slechter gescoord op de algemene gezondheidsschaal door de vitamine D insufficiëntie vrouwen ($p = 0.035$). Deze bevinding berust waarschijnlijk op toeval of het effect van multipele testen, omdat dit verschil niet bij de vrouwen werd gevonden die borstvoeding gaven.

Concluderend kan gesteld worden dat vitamine D status bij postpartum vrouwen niet geassocieerd is met het geven van borstvoeding of flesvoeding, gezondheidsstatus en vermoeidheid.

Hoofdstuk 5

Hoofdstuk 5 beschrijft de prevalentie van vitamine B12 deficiëntie postpartum, gebaseerd op totaal vitamine B12 en het metabool actieve vitamine B12 (holotranscobalamine). Tevens werd de hypothese onderzocht dat er een verschuiving plaatsvindt richting holotranscobalamine in postpartum vrouwen met onvoldoende beschikbare totale vitamine B12. Bij 171 postpartum vrouwen werd de fractie van actief vitamine B12 (holotranscobalamine/totaal vitamine B12) tussen vrouwen met en zonder vitamine B12 deficiëntie vergeleken. Vitamine B12 deficiëntie liet een spontane verbetering zien van 60 – 75% binnen 48 uur postpartum, naar 6 – 10% bij 5 weken postpartum. De fractie van actief vitamine B12 was significant hoger bij vitamine B12 deficiënte vrouwen vergeleken met vrouwen die niet vitamine B12 deficiënt waren ($p < 0.0001$).

Concluderend lijkt er een verschuiving plaats te vinden in de richting van het metabool actieve holotranscobalamine bij vrouwen met onvoldoende beschikbare totale vitamine B12. Deze resultaten suggereren dat de veranderingen van postpartum vitamine B12 fysiologisch zijn en worden verklaard door redistributie.

Hoofdstuk 6

In hoofdstuk 6 zijn de resultaten beschreven van vergelijkend onderzoek om ijzer deficiënte postpartum te definiëren middels mean corpuscular volume (MCV) of reticulocyte hemoglobin content (CHr). In een prospectief cohort werden anemische vrouwen onderverdeeld in microcytair (MCV < 80 fL, n = 30) en normocytair (MCV ≥ 80 fL, n = 85), of lage CHr (< 28 pg , n = 30) en normale CHr (≥ 28 pg, n = 75). Slechts 36% van de anemische vrouwen was ijzerdeficiënt. Alle anemische vrouwen werden behandeld met ferrofumaraat met of zonder foliumzuur gedurende 4 weken. Er werd geen verschil gezien in stijging van hemoglobine tussen de ijzerdeficiënte en niet-ijzerdeficiënte groepen. De vrouwen met ijzerdeficiëntie toonden een significante verbetering in de richting van normalisatie van de ijzerparameters MCV en CHr, terwijl de niet-ijzerdeficiënte vrouwen deze verhoging niet toonden.

Concluderend kan door een combinatie van hemoglobine met MCV of CHr een daadwerkelijke ijzerdeficiëntie bij postpartum anemische vrouwen worden geïdentificeerd.

Hoofdstuk 7

In dit hoofdstuk zijn de resultaten van een gerandomiseerde gecontroleerde trial beschreven waarin 112 postpartum anemische vrouwen werden gerandomiseerd om

600 mg ferrofumaraat en 1 mg foliumzuur per dag te ontvangen (n = 48) of alleen 600 mg ferrofumaraat per dag (n = 43) gedurende 4 weken. Na behandeling werden geen verschillen tussen beide groepen waargenomen in hemoglobine, gezondheidsstatus en vermoeidheid. Ongeveer 75% van alle vrouwen meldde ten minste één bijwerking ten gevolge van ferrofumaraat gebruik. Constipatie veroorzaakt door ferrofumaraat was significant geassocieerd met het staken van ferrofumaraat inname (p = 0.014).
Concluderend werd er geen toegevoegde waarde gezien van foliumzuur naast orale ijzer suppletie bij de behandeling van postpartum anemie ten aanzien van hematologische parameters, gezondheidsstatus en vermoeidheid.

Hoofdstuk 8
In hoofdstuk 8 worden de algemene discussie, conclusies en klinische implicaties van dit proefschrift weergegeven. De rol van vitamine D, anemie, ijzer, foliumzuur en vitamine B12 in associatie met gezondheidsstatus en vermoeidheid worden hierin uitgewerkt.

Vitamine D insufficiëntie komt voor bij ongeveer 60% van de postpartum vrouwen en is niet geassocieerd met de gezondheidsstatus, vermoeidheid en het geven van borst- of flesvoeding. Omdat de pasgeborene afhankelijk is van de vitamine D voorziening in de moedermelk, dient vitamine D suppletie te worden toegepast bij vrouwen die borstvoeding geven.
Postpartum anemie, gebaseerd op hemoglobine alleen, is niet geassocieerd met gezondheidsstatus en vermoeidheid. De behandeling van postpartum anemie bestaat veelal uit orale ijzersuppletie met of zonder foliumzuur suppletie. Echter, het toevoegen van foliumzuur aan deze ijzersuppletie bij de behandeling van postpartum anemie is niet zinvol met betrekking tot hemoglobine, gezondheidsstatus en vermoeidheid in ontwikkelde landen. Daarnaast blijkt slechts 36% van de vrouwen met postpartum anemie een ijzerdeficiëntie te hebben. Om overbehandeling en onnodige bijwerkingen te voorkomen, dient ijzersuppletie alleen te worden toegepast bij postpartum anemische vrouwen met een ijzerdeficiëntie. Door een combinatie van hemoglobine met MCV of CHr kunnen deze vrouwen worden geïdentificeerd
Vitamine B12 deficiëntie komt veel voor direct postpartum, maar verdwijnt spontaan vijf weken postpartum. Deze verandering is fysiologisch en toe te schrijven aan redistributie. Postpartum vrouwen zonder risicofactoren of manifestaties van een daadwerkelijke vitamine B12 deficiëntie, hebben geen vitamine B12 suppletie nodig.

Chapter 10

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List of publications

Dankwoord

Curriculum Vitae

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Curriculum Vitae

Daisy van der Woude werd geboren op 23 februari 1982 in Tilburg. Na het behalen van haar HAVO diploma in 1999 aan het Pauluslyceum in Tilburg, behaalde ze in 2000 haar propedeuse voor HBO verpleegkunde aan de Fontys Hogeschool in Tilburg. Daarna volgde zij in de avonduren natuurkunde en scheikunde op VWO niveau bij het ROC Midden Brabant college in Tilburg, waarvoor zij in 2001 haar diploma kreeg. Overdag werkte zij bij de thuiszorg in Tilburg totdat zij in 2002 kon beginnen aan de studie geneeskunde aan het Radboud Universiteit Nijmegen.

Tijdens haar coschap Gynaecologie en Obstetrie werkte Daisy in het TweeSteden ziekenhuis in Tilburg. Vanuit haar PICO presentatie werd het onderwerp voor haar promotieonderzoek geboren. Haar wetenschappelijke stage combineerde zij met haar keuze coschappen, waardoor zij 5 maanden op de afdeling Gynaecologie en Obstetrie in het TweeSteden ziekenhuis werkzaam was en daarnaast haar promotieonderzoek kon opstarten. In september 2008 behaalde zij haar artsexamen.

Van september 2008 tot en met september 2010 werkte zij als arts-assistent niet in opleiding op de afdeling Gynaecologie en Obstetrie van het TweeSteden ziekenhuis. Van september 2010 tot april 2011 had zij een aanstelling voor fulltime promovendus bij Tilburg University. Vanaf april 2011 is zij in opleiding tot gynaecoloog. De opleiding werd gestart in het Atrium Medisch Centrum in Heerlen (opleider Dr. F.J. Roumen, plaatsvervangend opleider Dr. P.E.A.M. Mercelina) en vanaf juli 2012 voortgezet in het Maastricht Universitair Medisch Centrum (opleider Prof. dr. R.F.P.J. Kruitwagen, plaatsvervangend opleider Dr. G.A.J. Dunselman). In februari 2015 keerde zij terug voor de opleiding naar het Atrium Medisch Centrum in Heerlen (opleider Dr. P.E.A.M. Mercelina, plaatsvervangend opleider Dr. N.A.C. Smeets).

Daisy is sinds augustus 2007 gelukkig samen met Arnoud voor de Poorte.